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Improved Preparation of α,*N*-Diphenylnitrones and *N*-Benzyl-*N*-Phenylhydroxylamines by direct Oxidation of Secondary Anilines

John W. Gorrod*[+)] and Nigel J. Gooderham[++)]

[+)] Department of Pharmacy, Chelsea College, University of London, Manresa Road, London, SW 3 6LX, G.B. [++)] Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota, 55455, U.S.A.

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A simple and rapid method for the oxidation of secondary anilines to α,*N*-diphenylnitrones and the subsequent reduction to secondary *N*-benzyl-*N*-phenylhydroxylamines is described.

Verbesserte Synthese von α,N-Diphenylnitronen und N-Benzyl-N-phenylhydroxylaminen durch direkte Oxidation von sekundären Anilinen

Es wird über eine einfache und schnelle Methode der Oxidation von sekundären Anilinen zu α,*N*-Diphenylnitronen und deren nachfolgende Reduktionen zu sekundären *N*-Benzyl-*N*-phenylhydroxylaminen berichtet.

To facilitate our studies of the metabolism of *N*-alkylanilines, authentic samples of *N*-oxidised derivatives were required to help identify and quantitate metabolites. However, examples of such compounds are few and the literature on their chemical properties differ. *Renner*[1)] reviewed the synthesis of *N*-methyl-*N*-phenylhydroxylamine in an attempt to resolve the conflicting reports concerning this compound. Attempted preparations included the reactions of methyl halides and dimethyl sulphate with phenylhydroxylamine[2)], of nitro compounds with *Grignard* reagents[3)] and hydrolysis and deamination of *N*-methyl-*N*-acetoxy-4-aminoaniline[4)]. More recently, the preparation of *N*-methyl-*N*-phenylhydroxylamine has been reported in which a modified *Cope* elimination procedure was employed with *N*-methyl-*N*-ethylaniline-*N*-oxide[5,6)]. No isolation or identification data were reported as the product was very unstable. The preparation of *N*-ethyl-*N*-phenylhydroxylamine and the 4-tolyl derivative were first described by *Utzinger* and *Regenass*[7)], and repeated by *Renner*[1)]. The products, obtained by the action of alkylhalide on the appropiate phenylhydroxylamine, were very unstable. The same authors also reported the synthesis of *N*-n-butylphenylhydroxylamines and *N*-benzyl-*N*-phenylhydroxylamine using similar techniques[7,1)]. An alternative approach to preparing *N*-substituted phenylhydroxylamines was adopted by *Calder* and *Forrester*[8)], who reacted *Grignard* reagents with 2-methyl-2-nitrosopropane to yield a series of *N*-t-butyl derivatives. Methods commonly used for the synthesis of *N,N*-disubstituted hydroxylamines generally require rigorous conditions[9)]. However, when one of the nitrogen substituents is a phenyl group, the required molecule is often unstable, and considerable difficulty has been experienced in the preparation of such simple *N*-alkyl-*N*-phenylhydroxylamines. In the majority of successful methods, preparation of the desired product was achieved using phenylhydroxylamine derivatives and alkylhalide. In nearly every case the resulting reaction was lengthy and subsequent isolation and purification of the product difficult.

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The *N*-alkyl-*N*-phenylhydroxylamines are readily converted to the corresponding nitrones*); often this occurs spontaneously. The formation of α-methyl-*N*-phenylnitrone and α-propyl-*N*-phenylnitrone were accomplished by oxidation of the corresponding disubstituted hydroxylamine with potassium hexacyanoferroate (III)[7,1]. The condensation of aldehyde and phenylhydroxylamine has been used to prepare α-propyl-*N*-phenylnitrone[10,1] and α,*N*-diphenylnitrone[11]. More specific methods have been used when a particular product (but not a series of products) is required.
The condensation of aromatic nitroso compounds with activated methylene or methyl groups as in the *Kröhnke* reaction[12,13], the reaction of nitrosobenzene with phenylhydrazone according to *Berry, Bryant, Smith* and *Landolt*[14], and the alkylation of oximes as described by *Brady, Dunn* and *Goldstein*[15], and *Beuhler*[16], have all been used to prepare nitrones. In the last case, the product of these reactions was invariably a mixture of oxime ether and nitrone depending on the nature of the starting oxime, alkylhalide and experimental conditions. Synthesis of the nitrones required for our studies would necessitate the formation of a phenylnitrogen linkage *via* arylating agents. As arylhalides are unreactive towards nucleophiles this method was not further considered.
Attempts in this laboratory to synthesise *N*-alkyl-*N*-phenylhydroxylamines and α-alkyl-*N*-phenylnitrones using the aforementioned procedures were tedious and often resulted in oils comprising complex mixtures. Exceptions were the preparation of α-phenyl-*N*-(4-substituted) phenylnitrones from benzaldehyde and 4-substituted phenylhydroxylamines according to *Bamberger*[17], although the initial synthesis of 4-substituted phenylhydroxylamines often required some degree of care due to the facile decomposition of these products.

Beckett, Coutts and *Ogunbona*[18] have described the preparation of a number of aralkyl nitrones and the corresponding disubstituted hydroxylamines from the parent amines[18] in which the initial step is a direct oxidation of a secondary aliphatic amine. Oxidation of substituted amines generally leads to multiple products. However, in these cases, the reaction involved controlled oxidation using 3-chloroperoxybenzoic acid (3-CPBA) to yield a mixture of nitrone and ester. Reduction of the reaction mixture (ester and nitrone) produced disubstituted hydroxylamines in good yields.

The disubstituted aliphatic hydroxylamine was found to be readily convertible back to the corresponding nitrone by mercuric oxide. The apparent ease and specificity with which this reaction proceeded prompted us to investigate the general applicability of this reaction in preparing the aryl,alkyl-*N*,*N*-disubstituted hydroxylamines required for our metabolic studies.

Results and Discussion

The reaction of 3-CPBA on 4-substituted *N*-benzylanilines produced good yields of α,*N*-diphenylnitrones in a relatively pure form. Acetone was the solvent of choice for the oxidation; dry acetone was found to produce higher yields and a purer product. Substitution of diethylether or halogenated solvents led to lower yields of nitrone and often a complex mixture of products. One explanation for this may be formation of the isomeric oxaziridine in preference to the nitrone. Such a compound would probably be reactive and lead to the formation of other products. Reaction temperatures greater than 5° and exposure to light increased the formation of unwanted side products. These facts are consistent with the reports that α,*N*-diphenylnitrone irradiated with UV light yielded first the isomeric oxaziridine then benzylidene aniline, benzaldehyde, nitrosobenzene and benzanilide[19,20]. The molar ratio of 3-CPBA to secondary aniline was found to be

important. With a ratio of less than 2 : 1, yields are not maximised and with a ratio greater than 2 : 1, further oxidation occurs and nitroso compounds are apparently produced as indicated by the intense blue or green colourations of the reaction mixture. Optimised conditions give a rapid reaction with easy isolation of the desired product in good yield.

The comparative stability and availability of the starting material (secondary aniline) gives considerable advantage over the alternative synthesis employing phenylhydroxylamine and benzaldehyde where the reactive nature of the hydroxylamine demands it being freshly prepared prior to use.

Analytical data presented in the experimental section confirm the purity and authenticity of the compounds prepared. NMR analysis confirmed the structures. Chemical shifts are as expected on the basis of the findings of *Beckett, Coutts* and *Ogunbona*[18]. The IR spectrum showed a band at 1170 cm^{-1} consistent with literature values for N — O stretching bands characteristic of nitrones[21,22,19]. The UV spectra of nitrones exhibited characteristic maxima at about 230 nm, plus the expected bathochromic shifts to about 330 nm upon conjugation with the aromatic ring[22,23].

The preparation of disubstituted hydroxylamines from the corresponding nitrones was accomplished by reduction with $LiAlH_4$[24]. A molar ratio of LAH to nitrone of 1 : 1 was found to be critical. An excess of LAH reduced the nitrone to the secondary aniline *via* the hydroxylamine. Heat invariably led to decomposition of the hydroxylamine, therefore the reactions were carried out at 20°.

The analytical data for the prepared hydroxylamines confirmed their structure. The NMR spectra are quite different from those of the corresponding nitrone, in particular the peak due to the N–OH group at δ = 5.8–6.0 ppm. Shaking the hydroxylamine with D_2O caused the disappearance of this peak. The UV and IR spectra of the compounds were also consistent with that of hydroxylamines, and were quite distinct from those of the corresponding nitrones. In addition, the hydroxylamines gave an immediate reaction with *Tollens* reagent and with ferric chloride and bathophenanthroline(4,7-diphenyl-1,10-phenanthroline).

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Experimental Part

Preparation of α-Phenyl-N-(4-substituted) phenylnitrones

To a cooled (0–5°) solution of the N-benzyl-4-substituted aniline (0.01 mol) in 25 ml dry acetone kept in the dark was added dropwise a solution of 3-CPBA (0.02 mol, 3.5 g) in 25 ml dry acetone over 1 h. The reaction was terminated by removal of the solvent i.vac. to leave an orange/yellow solid. The solid was dissolved in 50 ml diethylether containing a small quantity of dichloromethane. The ethereal solution was washed with aqueous potassium carbonate (0.5 M, 3 × 25 ml), distilled water (25 ml), dried (anhydrous $MgSO_4$) and concentrated i.vac. to leave a yellow feathery solid. Trituration of the solid with ice cold diethylether afforded white feathery crystals of α-

phenyl-*N*-(4-substituted) phenylnitrone. The product, recrystallised from hot diethylether was obtained in yields from 55–70 %. In all cases, TLC examination showed a single product.

α-*N-Diphenylnitrone* recovered as white feathery needles, m.p. 112–113°, lit.[25]: 112°.IR: 1170 cm^{-1}, UV (methanol) λ max = 227, 315 nm. M.S.: m/e = 197 (15 %M^+), 91 (100 %). ^{1}H-NMR: ($CDCl_3$): δ (ppm) = 7.35 (m. 6H, meta and para on both phenyl rings), 7.75 (m, 2H, ortho on N-phenyl ring), 7.92 (s, 1H, CH=N), 8.4 (m, 2H, ortho on α-phenylring).

α-*Phenyl-N-(4-chlorophenyl)nitrone* was recovered as cream feathery needles, m.p. 176–177°, lit.[23]: 181°. IR: 1170 cm^{-1}. UV (methanol) λ max = 228, 254, and 318 nm. M.S.: m/e = 233 (3 %), 231 (10 % M^+), 125 (100 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.38–7.85 (dd, 4H, N-phenyl protons), 7.5 (m, 3H. meta and para on α-phenyl), 7.92 (s, 1H, CH=N), 8.4 (m, 2H, ortho on α-phenyl).

α-*Phenyl-N-(4-tolyl)nitrone*, white feathery needles, m.p. 127–128°, lit.[26]: 124°. IR: 1170 cm^{-1}. UV (methanol) λ max. = 236, 251, and 316 nm. M.S.: m/e = 211 (15 % M^+), 105 (100 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.38 (s, 3H, CH_3), 7.15–7.75 (dd, 4H, N-phenyl protons), 7.45 (m, 2H, meta and para on α-phenyl), 7.9 (s, 1H, CH=N), 8.4 (m, 2H ortho on α-phenyl).

Preparation of N-benzyl-(4-substituted)-phenylhydroxylamine

α-Phenyl-N-(4-substituted)phenylnitrone (0.01 mol.) was dissolved in 150 ml of warm dried ether and added dropwise over a 30 min period to a stirred suspension of $LiAlH_4$ (0.01 mol, 0.38 g) in diethylether. The mixture was stirred for a further 20 min then the reaction terminated by adding dropwise water, 15 % sodium hydroxide, and additional water to yield a granular precipitate. The ethereal solution was filtered and the precipitate washed with 3 × 25 ml warm diethylether. The combined ether extract was dried (Na_2SO_4), and evaporated to dryness under reduced pressure to yield a creamy coloured solid. Recrystallisation from petroleum ether (b.p. 40–60°) afforded the disubstituted hydroxylamine as creamy white or slightly yellow needles. These concentrations and recrystallisation were carried out in the dark. Occasionally the final product was contaminated with small quantities of nitrone and parent amine. These impurities could be removed by washing the solid with cold (–20°) petroleum ether (b.p. 40–60°) to remove the amine, then washing with cold (–20°) diethyl ether, to leave the insoluble nitrone. The ethereal solution was evaporated in the dark under reduced pressure to dryness and the disubstituted hydroxylamine recrystallised from petroleum ether (b.p. 40–60°).

N-benzyl-N-phenylhydroxylamine recovered as white needles, m.p. 85–86°, lit.[25]: 86°. IR: 3550 cm^{-1}. UV (methanol): λ max. = 212 and 245 nm. M.S.: m/e = 199 (11 % M^+), 91 (100 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 4.8 (s, 2H, CH_2–N), 6.02 (s, 1H, N–OH-lost on shaking with D_2O), 7.2 (s, 4H, ortho phenyl rings), 7.3 (s, 6H rest of aromatic protons).

N-benzyl-N-(4-chlorophenyl)hydroxylamine, cream needles, m.p. 94–95°, IR: 3550 cm^{-1}. UV (methanol): λ max. 213 and 253 nm. M.S.: m/e = 235 (1 %), 233 (3 % M^+), 91 (100 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 4.28 (s, 2H, CH_2–N), 5.84 (s, 1H, N–OH-lost on shaking with D_2O). 7.15 (d, 4H, ortho and meta on N-phenyl ring), 7.3 (s, 5H protons on α-phenyl ring). $C_{13}H_{12}NOCl$ (233, 70) Calcd.: C 66.8 H 5.18 N 6.0; Found: C 66.5 H 5.17 N 6.0.

N-benzyl-N-(4-tolyl)hydroxylamine, white needles, m.p. 64–66°, IR: 3550 cm^{-1}. UV (methanol): λ max. = 213 and 247 nm. M.S.: m/e = 213 (7 % M^+), 91 (100 %). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.3 (s, 3H, CH_3), 4.35 (s, 2H, CH_2–N), 5.92 (s, 1H, N–OH-lost on shaking with D_2O). 7.08 (s, 4H ortho and meta on N-phenyl ring), 7.3 (s, 5H protons on α-phenyl ring). $C_{14}H_{15}NO$ (213,28) Calcd.: C 78.8 H 7.09 N 6.6; Found: C 78.6 H 6.96 N 6.7.

Materials and analytical methods: MP: uncorr. *IR:* Infracord IR spectrophotometer as Nujol mulls. *UV:* Pye Unicam SP800 spectrophotometer (methanol). *^{1}H-NMR spectra:* Perkin Elmer R32 90 mHz (deuterated chloroform, TMS int. stan.). Direct inlet *mass spectra*: VG 12F mass spectrometer, ionisation potential of 70 ev, source temp. 200–240°.

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*) Nitrone nomenclature used is that of C.A. where the prefix α is used for groups attached to the C atom and N for groups attached to the nitrogen.

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