glyoxal diethyl acetal (lit.[14] mp 125 °C). The mixture melting point of the two materials remained undepressed.

***trans*-2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-ethane (2d).** N_b-Benzyltryptophan methyl ester hydrochloride (**1b**; 4.05 g, 11.7 mmol) and propionaldehyde (**2d**; 1.0 mL, 13.7 mmol) were dissolved in a solution of methanol/water [75/25 (v/v), 70 mL]. The resulting mixture was refluxed (cold-finger condenser, dry ice–chloroform) for 48 h under nitrogen. The reaction was cooled and the solvent removed under reduced pressure. The oil which remained was taken up in chloroform and washed successively with ammonium hydroxide (14%, 50 mL) and brine solution. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oil which remained was chromatographed on silica gel (100 g) to provide the *trans*-1,3-disubstituted-tetrahydro-β-carboline (**3d**, 3.25 g) in 80% yield: mp 149–150 °C (methanol); IR (KBr) 3380 (s), 1725 (s) cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, t, *J* = 7.0 Hz), 1.72 (2 H, q, *J* = 7.0 Hz), 3.05 (2 H, d, *J* = 7 Hz), 3.50 (3 H, s), 3.53–4.10 (4 H, m), 7.00–7.70 (10 H, m); mass spectrum (indirect inlet, EI), *m/e* 348 (M$^+$, 1%), 346 (1), 344 (1), 319 (17), 121 (23), 91 (97).

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.56; H, 7.46; N, 8.17.

***trans*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-ethane (4d).** *trans*-N_b-Benzyl-1-ethyl-3-(carbomethoxy)tetrahydro-β-carboline (**3d**; 0.50 g, 1.44 mmol) was dissolved in a solution of methanol (200 mL) and glacial acetic acid (30 mL). The mixture was subjected to catalytic hydrogenation (Parr, 500 mL) over a Pd/C catalyst (0.050 g, 5%) at 50 psi for 20 h. TLC indicated the presence of only one material (R_f 0.20, silica gel, 1% methanol–chloroform); therefore the catalyst was filtered from the solution and the solvent was removed under reduced pressure. The oil which remained was dissolved in chloroform (250 mL) and the organic layer washed successively with ammonium hydroxide solution (80 mL, 14%) and brine. The organic layer was dried (Na_2SO_4), after which the solvent was removed under reduced pressure and the oil which remained was crystallized from hot methanol to provide the *trans*-1-ethyltetrahydro-β-carboline (**4d**, 155 mg). Recrystallization of the mother liquors gave additional quantities of **4d** (190 mg, combined yield 345 mg, 97%), mp 152–153 °C (lit.[14] mp 152–153 °C). The R_f and IR, proton NMR, and carbon NMR spectra of the trans derivative were identical with those previously reported for *trans*-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-ethane[14] whose structure had been proven by carbon NMR and single-crystal X-ray analysis.[14] The mixture melting point of **4d** showed no depression.

Acknowledgment. This work was generously supported by a grant (HL 17897) from the National Heart and Lung Institute and by an NIH Biomedical Sciences award to U.W.M. We thank both the Research Corporation and the Graduate School for support of the initial phases of this investigation. Special thanks to Mr. Frank Laib, Mr. Noel Whittaker, and Ms. Gail Boviall for technical assistance are in order.

Registry No. 1a, 73327-10-3; **1b**, 19779-78-3; **2b**, 2043-61-0; **2d**, 123-38-6; **3b**, 73327-01-2; **3c**, 75522-09-7; **3d**, 73327-04-5; **4b**, 73327-06-7; **4c**, 75140-18-0; **4d**, 73327-08-9.

Notes

Interaction of Phenylhydrazones with Nitrosobenzene-Radical Intermediates

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Nitrones, along with benzene and nitrogen, are produced from the reaction of nitrosobenzene (1) and phenylhydrazones.[1] This reaction has been shown to follow second-order kinetics, and rates of reactions utilizing reactants substituted on meta and para positions of each of the three available aromatic rings have been correlated by using the Hammett treatment.[2] Yields of nitrones (based on phenylhydrazone) produced from this reaction have been found to be diminished in a nitrogen atmosphere vs. air, but use of excess nitrosobenzene resulted in higher yields. On the basis of these observations, the mechanism for the reaction of benzaldehyde phenylhydrazone (BPH, 2) in Scheme I has been proposed.[1]

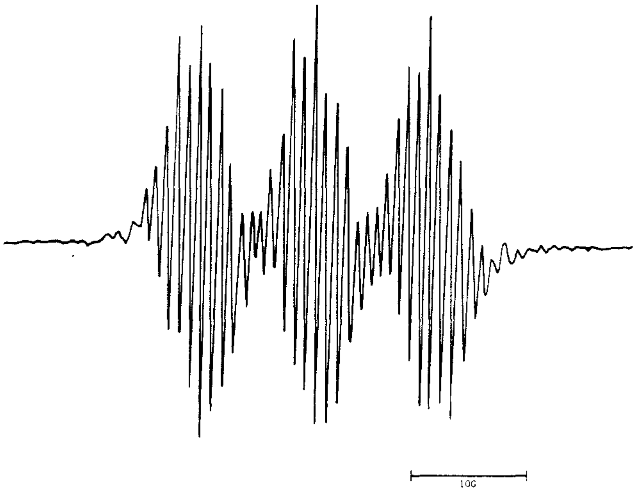

Figure 1. EPR spectrum from 1:2 BPH/nitrosobenzene reaction.

Phenyldiazene (**5**) is a short-lived, oxygen-sensitive species known to decompose to benzene and nitrogen via a bimolecular process, reportedly not including free radicals.[3] A possible modification of Scheme I, that also would account for benzene and nitrogen production, involves decomposition of intermediate **3** by a radical process. Hydroxyl hydrogen abstraction from **3** would yield nitroxide **6**, which, by reversal of a spin-trapping reaction, could yield nitrone **4** and phenyldiazo radical, $PhN_2\cdot$. The latter is a potential source of nitrogen and phenyl radicals.

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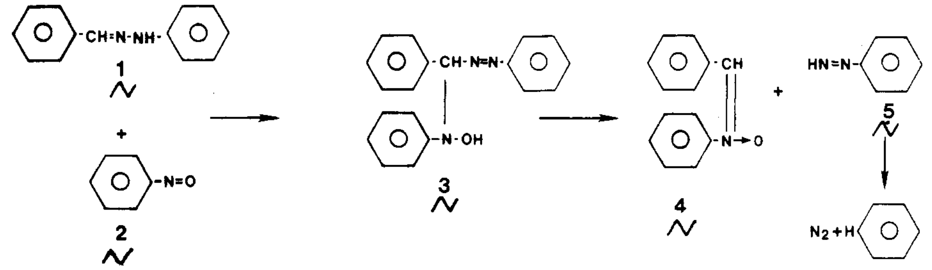
[1] Berry, D. W.; Bryant, R. W.; Smith, J. K.; Landolt, R. G. *J. Org. Chem.* **1970**, *35*, 845.

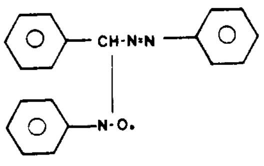
[2] DellaColetta, B. A.; Frye, J. G.; Youngless, T. L.; Zeigler, J. P.; Landolt, R. G. *J. Org. Chem.* **1977**, *42*, 3057.

[3] (a) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193. (b) A more recent report states that free radicals are involved in phenyldiazene decomposition: Galland, R.; Heessing, A.; Kaiser, B. U. *Justus Liebigs Ann. Chem.* **1976**, 97–111; *Chem. Abstr.* **1976**, *84*, 134841.

Scheme I



The present study represents efforts to determine the degree that free radicals are involved in this reaction system. Specifically, byproduct analysis has provided strong evidence for phenyl radical intermediacy. Careful column chromatography of reaction mixtures produced when BPH was allowed to interact with excess nitrosobenzene in a nitrogen atmosphere resulted in isolation of α,α,*N*-triphenylnitrone, $Ph_2C=N(O)Ph$, as a byproduct of nitrone 4, sometimes in yields in excess of 10%. The triphenylnitrone is known to be derived from reaction of 4 with phenyl radicals, probably via the nitroxide intermediate 7.[4]



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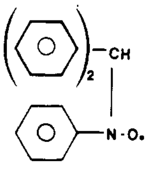

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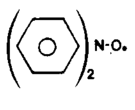

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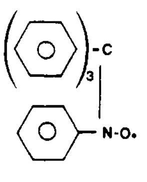

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Further evidence for the presence of phenyl radicals in this system was derived from isolation of bromobenzene in moderate yield from reaction of BPH with nitrosobenzene in the presence of bromotrichloromethane. However, it should be noted that bromobenzene may result either from attack by phenyl radical on bromotrichloromethane or reaction of the latter with phenyldiazene.[5]

Conclusive evidence for the presence of free-radical intermediates in the BPH/nitrosobenzene reaction system came from electron paramagnetic resonance studies. A strong EPR signal was obtained from nitrogen-flushed reaction mixtures. The complex pattern of this spectrum is virtually coincident with that reported for diphenyl nitroxide 8.[6] The same basic EPR spectrum resulted from 1:1 and 1:2 mixtures of BPH and nitrosobenzene; the spectrum observed for the 1:2 reaction is shown in Figure 1 (α^{N} = 9.5 G, $\alpha^{H}_{o,p}$ = 1.8 G, α^{H}_{m} = 0.9 G). The spectrum is quite unlike that reported for nitroxides with α hydrogens, such as 7.[7]

An EPR spectrum was also observed for a 1:1 mixture of benzophenone phenylhydrazone and nitrosobenzene. In this system, trapping of phenyl radicals by nitrosobenzene would again give nitroxide 8, whereas trapping by α,α,*N*-triphenylnitrone should yield nitroxide 9. The pattern actually observed is very similar to Figure 1 (diphenyl nitroxide), and the spectrum is significantly more complex than that reported for phenyl trityl nitroxide 9, where splitting is influenced by protons on only one adjacent phenyl ring.[8]

These results suggest that phenyl radicals are generated in reactions of BPH and nitrosobenzene and that depletion of nitrosobenzene by phenyl radicals is a major factor leading to reduced yields of nitrones in reactions employing equal amounts of 1 and 2, under nitrogen. When present in significant amounts, nitrone 4 also may trap phenyl radicals, but resulting nitroxide 7 may be further oxidized to α,α,*N*-triphenylnitrone and thus not noticeably influence EPR spectra.

Experimental Section

Materials and Equipment. Reagents were obtained as described previously.[1,2] Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained by using a Beckman IR-20A spectrophotometer, and gas chromatographic analyses were accomplished by using a Beckman GC-2 instrument with a 6 ft × 0.25 in. SE-30 column and thermal-conductivity detector. A Varian 4500 EPR spectrometer was used to obtain electron paramagnetic resonance spectra of samples in a thin-walled, quartz EPR tube (J. S. Scanlon, Co.). A degassed 0.0015 M solution of α,α-diphenyl-β-picrylhydrazyl was used as an external standard for derivation of hyperfine splitting constants (α^{N} = 9.0 G).[9]

α,*N*-Diphenylnitrone and α,α,*N*-Triphenylnitrone. A 45-mL portion of benzene in a side-arm dropping funnel was flushed with dry nitrogen, and 15 mL was dropped into a three-necked flask containing 0.196 g (1.00 mmol) of benzaldehyde phenylhydrazone. Nitrosobenzene, 0.214 g (2.00 mmol), was dissolved in the benzene remaining in the dropping funnel and added to the BPH solution; the nitrogen flush was maintained in the funnel and the three-necked flask throughout the addition and for a subsequent 2-h period. The reaction mixture was reduced in volume by rotary evaporation and carefully chromatographed on silica gel. Elution with benzene brought off 0.159 g (0.81 mmol) of α,*N*-diphenylnitrone. Elution with 20% ethyl acetate in benzene yielded 0.029 g (0.11 mmol) of α,α,*N*-triphenylnitrone. Slightly lower yields (73% diphenylnitrone and 7.3% triphenylnitrone) were obtained from a reaction by using more solvent (100 mL) and a 4-h reaction period.

In reactions under nitrogen using 1.00 mmol of each reactant, yields of diphenylnitrone ranged from 59–65%, and only traces of triphenylnitrone were isolated. Significant amounts (~100 mg) of unchanged benzaldehyde phenylhydrazone, contaminated with intractable material, were also recovered in early chromatography cuts. α,α,*N*-Triphenylnitrone was characterized by its

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[4] Iwamura, M.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 856.

[5] Huyser, E. S.; Wang, R. H. S. *J. Org. Chem.* **1968**, *33*, 3901.

[6] (a) Fischer, P. H. H.; Naugebauer, F. A. *Z. Naturforsch., A* **1964**, *19*, 1514 (α^{N} = 9.66 G, α^{H}_{o} = α^{H}_{p} = 1.83 G, α^{H}_{m} = 0.79 G). (b) Thomas, J. R. *J. Am. Chem. Soc.* **1960**, *82*, 5955 (α^{H} = 10.9 G, α^{H} = 0.9 G). (c) Chalfont, G. R.; Hey, D. H.; Liang, K. S. Y.; Perkins, M. J. *J. Chem. Soc.* **1971**, 233 (α^{N} = 9.7).

[7] Bluhm, A. L.; Weinstein, J. *J. Org. Chem.* **1972**, *37*, 1748.

[8] The trityl phenyl nitroxide spectrum is reported to show three groups of twelve lines: 1:2:1 triplets of approximately 1:3:3:1 intensity α^{N} = 10.93, $\alpha^{H}_{o,p}$ = 2.16, α^{H}_{m} = 0.8 G (Maender, O. W.; Janzen, E. G. *J. Org. Chem.* **1969**, *34*, 4072.

[9] Ueda, H.; Kuri, Z.; Shida, S. *J. Chem. Phys.* **1962**, *36*, 1676.

melting point of 218–220 °C (lit[10] mp 218–220 °C) and infrared spectrum, which was coincident with that of authentic material.[11]

Reaction of BPH with Nitrosobenzene in the Presence of $BrCCl_3$. Bromotrichloromethane, 0.396 g (2.0 mmol), was mixed with 0.107 g (1.0 mmol) of nitrosobenzene in 5 mL of nitrogen-flushed benzene and subsequently was treated with a solution of 0.196 g of BPH (1.0 mmol) in 15 mL of benzene, also deaerated with nitrogen. The reaction was allowed to proceed for 2 h under a N_2 atmosphere. Gas chromatographic analysis of the reaction mixture indicated the presence of 0.3 mmol of bromobenzene, using *o*-xylene as an internal standard. Bromotrichloromethane alone was observed to cause a dramatic color change in benzene solutions of BPH (yellow to deep orange), but GC analysis showed no bromobenzene resulting from this interaction.

EPR Analysis. Benzaldehyde Phenylhydrazone and Nitrosobenzene in Benzene. "Spectro"-grade benzene (10 mL) was flushed for 0.5 h in a side-arm dropping funnel, and 11 mg (0.1 mmol) of nitrosobenzene was added. A small aliquot was dropped directly into a quartz EPR tube; no EPR signal was noted. A 20-mg (0.1 mmol) sample of BPH was added to the original benzene solution, (nitrogen flush was maintained), and EPR analysis of an aliquot of this solution showed a strong, highly split signal within 20 min. When this procedure was repeated with 11 mg (0.10 mmol) of nitrosobenzene and 10 mg (0.05 mmol) of BPH, an EPR spectrum (Figure 1) nearly identical with that from the 1:1 reaction was observed.

Benzophenone Phenylhydrazone and Nitrosobenzene in Benzene. "Spectro"-grade benzene (10 mL) was degassed with nitrogen for 1 h, and 11 mg (0.1 mmol) of nitrosobenzene was added. EPR analysis of an aliquot showed no signal. After 26 mg (0.1 mmol) of benzophenone phenylhydrazone was added to the original solution, a strong, highly split EPR signal was observed within 15 min. This spectrum was very similar to that of Figure 1.

Acknowledgment. The support of this work through a National Science Foundation Undergraduate Research Participation Grant and a Cottrell College Science Grant from the Research Corporation is acknowledged gratefully. The assistance of Dr. Nathan L. Bauld in interpretation of EPR spectra is greatly appreciated.

Registry No. 1, 588-64-7; 2, 586-96-9; 4, 113-96-8; α,α-*N*-triphenylnitrone, 4504-13-6; benzophenone phenylhydrazone, 574-61-8.

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(10) (a) Ingold, C. K.; Weaver, S. D. *J. Chem. Soc.* **1924**, *125*, 1456. (b) Corrected identity: Burkhardt, G. N.; Lapworth, A.; Walkden, J. *Ibid.* **1925**, *127*, 2458.

(11) "Sadtler Standard Spectra"; Sadtler Research Laboratories: Philadelphia, 1970; infrared grating spectrum no. 2219.

Unusual Regioselectivity of Dichlorocarbene Addition to a Norbornene Derivative. X-ray Structure of the Stable Product

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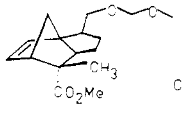
Received February 20, 1980

The reaction of dichlorocarbene with unsymmetrically substituted bicyclo[2.2.1]heptenes is well-known to yield a mixture of regioisometric 4-*exo* chlorides of bicyclo[3.2.1]oct-2-enes.[1] We report an instance of this reaction which displayed remarkable regioselectivity.

In the course of our work on a general synthesis for the cedrane sesquiterpenes, a model study was undertaken to provide a method for regiochemically controlling the ring expansion of ester 1 to the cedranoid skeleton, e.g., 2. Ester 3 was the origin of the model study and we anticipated that the reaction of 3 with dichlorocarbenes would yield a mixture of exo allylic chlorides 4 and 5. Surprisingly, when ester 3 was refluxed in benzene with the dichlorocarbene-generator phenyl(bromodichloromethyl)mercury,[3] only a single regioisomer was isolated in 80% yield. NMR spectral measurements and ^1H NMR decoupling experiments failed to differentiate between the two possibilities for this material and an X-ray structure was ultimately required to establish its identity as 5 (vide infra).



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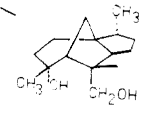

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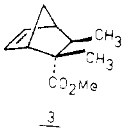

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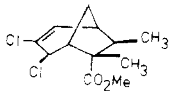

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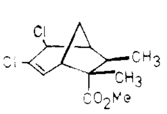

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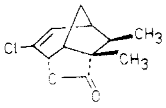

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As a means of defining regiochemistry, we had initially intended to transform the expected mixture of ring-expansion products into lactone 6 through displacement of chloride by the *endo*-carbonyl function, perhaps under solvolytic conditions.[4] In practice, 5 was stable to refluxing 10% H_2SO_4. However, refluxing with 10% aqueous potassium hydroxide afforded lactone 6 in 80% yield, apparently by an anti S_N2' reaction with carboxylate as an internal nucleophile.[5]

In order to determine whether production of a single allylic chloride was a function of the nature of the carbene generator, ester 3 was subjected to dichlorocarbene generated under phase-transfer conditions.[6] An ^1H NMR spectrum of the crude product displayed resonances indicative of the starting material, compound 5, and a third material in 1:2:1 ratio as determined by integration over the carbomethoxy absorptions, δ 3.6–3.8. The resonances attributable to this third component (NMR δ 6.19 (1 H, d, J = 7.0 Hz), 4.46 (1 H, d, J = 3.0 Hz), 3.72 (3 H, s)) suggested that it was the second exo chloride (4). Preparative-layer chromatography on silica gel with 20% ether–hexane provided three distinct bands from two of which were isolated starting material (R_f 0.9) and compound 5 (R_f 0.5). However, instead of a pure product, the third

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(1) (a) A. D. Wolf and D. G. Farnum, *J. Am. Chem. Soc.*, **96**, 5175 (1974); (b) C. W. Jefford, S. Mahajan, G. Waslyn, and B. Waegell, *ibid.*, 89, 2138 (1965).

(2) Previously prepared by K. Aldes, R. Hartmann, and W. Roth, *Chem. Ber.*, **93**, 2271 (1960), inter alios.

(3) D. Seyferth, J. Y.-P. Mui, and L. J. Todd, *J. Am. Chem. Soc.*, **86**, 2961 (1964).

(4) An examination of Dreiding models indicated that only one allyl group was accessible to the *endo*-carbonyl group. Thus, lactonization necessarily defines the relative positions of substituents.

(5) This ring expansion–lactonization sequence has been successfully applied to ester 1 in the total synthesis of 8*S*, 14-cedranediol (2): D. W. Landry, Dissertation, Harvard (1979), manuscript for publication in progress.

(6) T. Sasaki, S. Equchi, and T. Kiringama, *J. Org. Chem.*, **38**, 2230 (1973).