calcd for $C_{23}H_{26}N_2O_4$ 394.1893, found 394.1904 (100), 379 (35), 335 (73).

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Registry No. (±)-1, 116949-72-5; (±)-3, 84960-68-9; (±)-5 (X = H), 84960-69-0; (±)-5 (X = Cl), 116926-89-7; (±)-6 (X = Cl), 116912-01-7; (±)-7 (X = Cl), 116912-02-8; (±)-8 (X = Cl), 116912-03-9; (±)-9, 116912-04-0; (±)-10, 116912-05-1; (±)-11, 116912-06-2; (±)-12, 116926-90-0; (±)-13, 116912-07-3; (±)-14, 116912-08-4; CH_2=$CClCH_2I$, 39557-31-8.

Supplementary Material Available: Crystal data, fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond distances, and bond angles for 5 (X = H) and 5 (X = Cl) (27 pages). Ordering information is given on any current masthead page.

Conjugate Addition of *N,N*-Dialkylhydroxylamines: Mechanism of O-Alkylation by 1*H*-Pyrrole-2,5-diones

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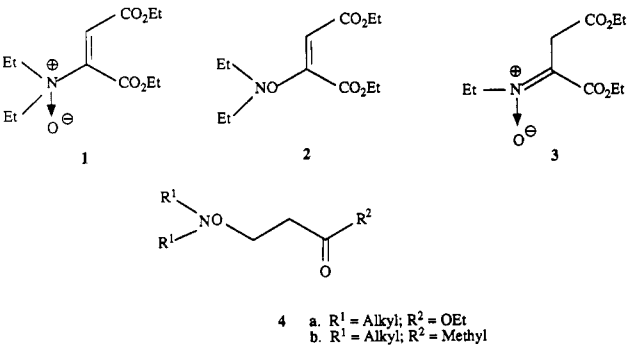
The addition of hydroxylamine to various activated C–C double bonds has been reported in the literature.[1-4] Quite recently, the conjugate addition of *N*-monoalkyl-substituted hydroxylamines to α,β-unsaturated esters was utilized by Baldwin in an elegant synthesis of isoxazolidin-5-ones,[5] which are of pharmacological interest.[6] The conjugate addition of the nitrogen atom of *N*-monoalkylhydroxylamines to the double bonds of pyrroles[7] and pyridones[8] is known.

The addition of *N,N*-dialkylhydroxylamines to acetylenedicarboxylate esters was reported by Winterfeldt and Krohn[9] to give initially the *N*-oxide adduct 1. The *N*-oxide 1, which was isolated in 84% yield, upon standing rearranged to a mixture of the O-alkylation product 2 and the nitrone 3 that were suggested to arise by a Meisenheimer rearrangement[10] and by a Cope elimination reaction[11] followed by hydrogen atom rearrangement, respectively. The suggestion that the conversion of 1 to 2 proceeds by a Meisenheimer rearrangement is surprising because the Meisenheimer rearrangement is facile only when the migrating group is allyl[12] or benzyl,[13] although the migration of neopentyl,[14] homoadamantyl,[15] and aryl[16] have been reported.[17] In contrast, Zinner and co-workers[18] reported that the products of direct O-alkylation 4a–b were obtained in the reaction of *N,N*-dialkylhydroxylamines with the activated C–C double bonds of acrylate esters and vinyl ketones, respectively. As recognized by Zinner,[18b] a mechanism involving the Meisenheimer rearrangement of a *N*-oxide adduct is highly unlikely in these cases because a Cope reaction due to the presence of a β-hydrogen atom is expected.[17] Zinner suggested that the observed products were the result of direct O-alkylation.

In view of both our interest in the addition of nucleophiles to 1*H*-pyrrole-2,5-diones,[19,20] commonly known as maleimides, and the apparent dichotomy reported in the literature, we report in this paper an investigation of the reaction of *N,N*-dialkylhydroxylamines with maleimides.



1 2 3

4 a. R^1 = Alkyl; R^2 = OEt
b. R^1 = Alkyl; R^2 = Methyl

Results and Discussion

The reaction of **5a** with the *N,N*-dialkyl-substituted hydroxylamine **6a** in a tetrahydrofuran (THF) reaction medium with potassium *tert*-butoxide as a basic catalyst led to a complex mixture of products. This result is no doubt attributable to the propensity of **5a** toward base-catalyzed oligomerization.[20-22] The uncatalyzed reaction of **5a** and **6a** in THF at reflux temperature gave **7a** as white crystalline solid (56% recrystallized).

The structure of **7a** rests on the following observations. In the IR spectrum of **7a**, two absorptions were observed at 1790 cm^{-1} (weak) and 1725 cm^{-1} (strong), which result from the asymmetrical and symmetrical C=O stretching modes. In the ^1H NMR spectrum of **7a**, a distinct ABX coupling pattern was observed with $^3J_{AX}$ = 5 Hz, $^3J_{BX}$ =

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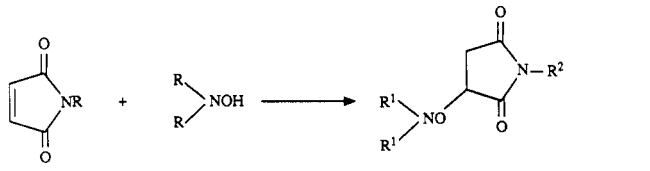
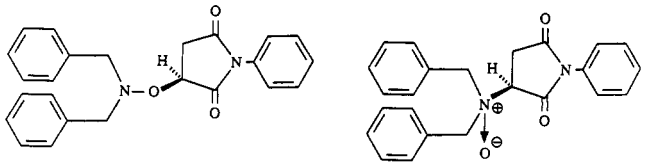


5 a. R = Phenyl; b. R = H; c. R = Methyl; d. R = Cyclohexyl; e. R = 1-Octadecyl

6 a. R = Benzyl; b. R = Ethyl

7 a. R^1 = Benzyl; R^2 = Phenyl; b. R^1 = Benzyl; R^2 = H; c. R^1 = Benzyl; R^2 = Methyl; d. R^1 = Benzyl; R^2 = Cyclohexyl; e. R^1 = Benzyl; R^2 = 1-Octadecyl; f. R^1 = Ethyl; R^2 = Phenyl

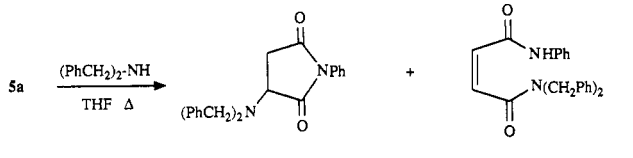
8 Hz, and $^2J_{AB}$ = 20 Hz. Quite surprisingly, however, the benzyl protons were observed as a distinct AB quartet with $^2J_{AB}$ = 12.5 Hz. The nonequivalence of the benzylic protons is of course expected because these protons are magnetically nonequivalent due to the adjacent stereogenic carbon atom in the pyrrole ring that is three bonds away.[23,24] The degree of nonequivalence, however, suggested the alternate *N*-oxide structure **8** in which the prochiral protons on the benzylic carbon atom are only two bonds removed from the asymmetric carbon atom of the pyrrole ring. Although the ^{1}H NMR spectral assignments would not be unreasonable for structure **8**, the observation of a molecular ion at 386 mass units without the observation of a M − 16 peak (loss of oxygen from the *N*-oxide) in the MS strongly suggests the aminoxy structure **7a**.



7a **8**

Although the spectral and elemental analyses were fully in accord with the product of O-alkylation, **7a**, the observation by Winterfeld[9] of the alternative *N*-oxide structure in the reaction of *N*,*N*-dialkylhydroxylamines with acetylenedicarboxylate esters pressed for a more rigorous proof of the structure. A unambiguous answer would be provided by the synthesis of an authentic sample of **8** by an established synthetic procedure.

To this end, the *N*,*N*-dibenzylamine adduct **9** along with the ring-opened product **10** was obtained by the reaction of **5a** with *N*,*N*-dibenzylamine in THF at reflux. The desired product **9** could be obtained by HPLC or flash chromatographic separation, albeit in low yield (16%).



9 **10**

The reaction of **9** with *m*-chloroperoxybenzoic acid[25] at −5 to 0 °C for 1 h gave none of the expected product **8**, but rather a mixture of **5a**, **6a**, and a small quantity of starting material **9**. A reasonable explanation of this observation is that **8** was generated upon oxidation of **9** and immediately underwent a Cope elimination reaction to give **5a** and **6a**. The identity of **6a** was established by ^{1}H NMR analysis and identical elution time on TLC with an authentic sample. The results of this experiment establish

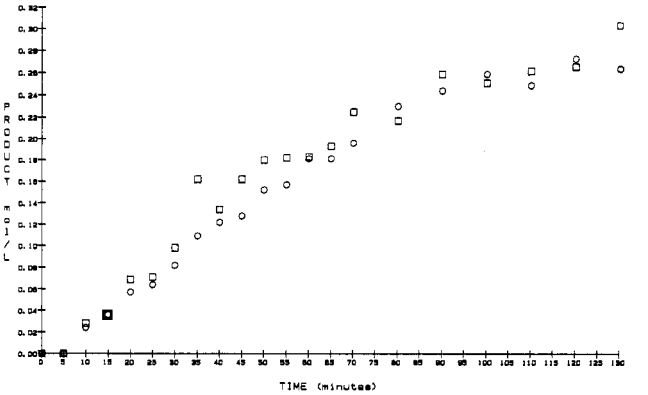


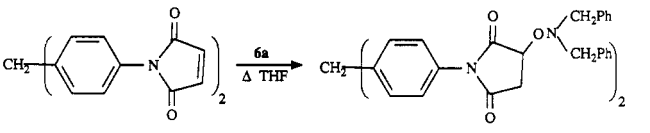
Figure 1. Formation of **7a** by the reaction of **5a** with **6a** at 65.5 °C as a function of time both in the presence and absence of *m*-dinitrobenzene. (○) Control; (□) 1.1 equiv of *m*-dinitrobenzene.

that **7a** is the product of O-alkylation. Furthermore, the absence of observable quantities of **7a** in the reaction mixture demonstrates that the *formation of* **7a** *is not due to a Meisenheimer rearrangement of* **8**. This must be the case because only the products of a Cope elimination reaction are observed from the in situ generated *N*-oxide **8**. If it occurs, N-alkylation must be a rapidly reversible process in the reaction of **5a** and **6a**. Indeed, when the reaction of **5a** with **6a** was monitored by ^{1}H NMR spectroscopy, the clean formation of **7a** was observed without any detectable resonances in the ^{1}H NMR spectrum attributable to the *N*-oxide **8**.

The formation of **7a** was monitored by ^{1}H NMR spectroscopy alone and in the presence of 1.1 equiv of *m*-dinitrobenzene, which is a powerful inhibitor of electron-transfer reactions (ET) that proceed through the intermediacy of radical anions.[26,27] No inhibition or change in the rate of formation of **7a** was observed in the presence of *m* dinitrobenzene (Figure 1), which strongly suggests that an ET mechanism is not operative. Although further mechanistic work is needed, the present results suggest that the mechanism of conjugate addition of **6a** to the activated double bond of **5a** is ionic in nature.

The O-alkylation of *N*,*N*-dialkylhydroxylamines by maleimides appears to be general. The reaction of maleimides **5a–e** with the hydroxylamines **6a–b** gave the corresponding O-alkylated products **7b–f** in good yield. That an *N*-aryl- or *N*-alkyl-substituent on the maleimide is not necessary was shown by formation of **7b** from **6a** and the unsubstituted maleimide **5b** (70% chromatographed).

In a similar manner, the bisadduct **12** was prepared by the reaction of **11**[28] with **6a** (61% recrystallized). In the case of the ortho and meta bismaleimides **13a–b**, the major products obtained were the expected bisadducts **14a** and **14c**, respectively, although a small quantity of the corresponding monoadducts were isolated by preparative HPLC.



11 **12**

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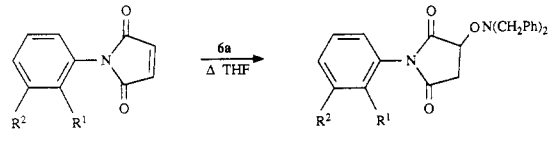
The results of this study together with those of Zinner[18] suggests that O-alkylation of *N,N*-dialkylhydroxylamines by activated double bonds is a general reaction and that N-alkylation is a fast reversible process, the product of which can be isolated in certain instances, as in the case of Winterfeldt.[9] The O-alkylation product **2** observed by Winterfeldt can be explained by elimination of dialkylhydroxylamine from **1** followed by subsequent O-alkylation without the necessity of a Meisenheimer rearrangement, which is consistent with the fact that in certain cases Winterfeldt observed only O-alkylation.[29] This explanation is further supported by the fact that in the present case products resulting from the Meisenheimer rearrangement of a benzyl moiety in the reactions with *N,N*-dibenzylhydroxylamine were not observed.



13

a. R^1 = 2,5-Dioxo-1*H*-pyrrol-1-yl
R^2 = H
b. R^1 = H
R^2 = 2,5-Dioxo-1*H*-pyrrol-1-yl

14

a. R^1 = 3-((N,N-Dibenzylamino)oxy)-2,5-dioxopyrrolidin-1-yl
R^2 = H
b. R^1 = 2,5-Dioxo-1*H*-pyrrol-1-yl
R^2 = H
c. R^1 = H
R^2 = 3-((N,N-Dibenzylamino)oxy)-2,5-dioxopyrrolidin-1-yl
d. R^1 = H
R^2 = 2,5-Dioxo-1*H*-pyrrol-1-yl

Experimental Section

All melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1300 spectrophotometer, and reported peak absorptions are estimated to be accurate to ±10 cm^{-1}. ^1H NMR spectra were taken on a JEOL FX-90Q, Varian Model CFT-20 or Varian Model XL-200 spectrometer. All ^1H chemical shifts are reported in ppm relative to tetramethylsilane where a positive sign is downfield from the standard. The abbreviations used for peak multiplicity are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, and dq = doublet of quartets. MS were obtained on a Finnegan Model 8200 mass spectrometer.

Whatman DSC-1F silica gel was used for all dry-column chromatography.[30] Merck 9385 silica gel 60 (230–400 mesh) was used for flash chromatography.[31] Merck precoated (0.25 mm) silica gel 60 F-254 plates were used for TLC. Preparative HPLC was carried out with a Waters PREP 500A HPLC.

Reagents were purchased from commercial laboratory supply houses. Solvents were dried prior to use when necessary with appropriate drying agents. Tetrahydrofuran (THF) was distilled immediately prior to use from a deep-blue solution of sodium ketyl (sodium/benzophenone). Reactions were carried out in flame-dried apparatus under a dry, inert atmosphere of either nitrogen or argon. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corp.

***N*-Phenyl-3-[(*N,N*-dibenzylamino)oxy]pyrrolidine-2,5-dione (7a).** A suspension of 6.0 g (28 mmol) of **6a** and 4.9 g (28 mmol) of **5a** in 50 mL of THF was heated at reflux temperature for 40 h. The solvent was removed in vacuo, and the residue was recrystallized from toluene to give 6.1 g (56%) of a white solid: mp 91–93 °C; IR (CH_2Cl_2) ν 1790, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (80 MHz) δ 2.09 (dd, 1 H, J_{AB} = 20 Hz, J_{AX} = 5 Hz), 2.13 (dd, 1 H, J_{BA} = 20 Hz, J_{BX} = 8 Hz), 3.90 (AB q, 4 H, $^2J_{HCH}$ = 12.5 Hz), 5.50 (dd, 1 H, J_{XA} = 5 Hz, J_{XB} = 8 Hz), 7.40 (complex m, 15 H). Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.6; H, 5.7; N, 7.3. Found: C, 74.6; H, 5.6; N, 7.2.

3-[(*N,N*-Dibenzylamino)oxy]pyrrolidine-2,5-dione (7b). By the procedure used to prepare **7a**, compound **7b** was prepared from 5.3 g (25 mmol) of **6a** and 2.4 g (25 mmol) in **5b** in 50 mL of THF (6 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 4:1, heptane–ethyl acetate eluent) to give 5.4 g (70%) of a colorless liquid: ^1H NMR ($CDCl_3$) (80 MHz) δ 1.81 (dd, 1 H, J_{AB} = 18 Hz, J_{AX} = 6 Hz), 2.25 (dd, 1 H, J_{BA} = 18 Hz, J_{BX} = 8 Hz), 3.88 (AB q, 4 H, $^2J_{HCH}$ = 12 Hz), 4.25 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} = 8 Hz), 7.35 (s, 10 H). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.7; H, 5.8; N, 9.0. Found: C, 69.9; H, 5.8; N, 9.0.

***N*-Methyl-3-[(*N,N*-dibenzylamino)oxy]pyrrolidine-2,5-dione (7c).** By the procedure used to prepare **7a**, compound **7c** was prepared from 5.3 g (25 mmol) of **6a** and 2.8 g (25 mmol) of **5c** in 50 mL of THF (24 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 4:1, heptane–ethyl acetate eluent) to give 7.6 g (94%) of a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.88 (dd, 1 H, J_{AB} = 18 Hz, J_{AX} = 8 Hz), 2.31 (dd, 1 H, J_{BA} = 18 Hz, J_{BX} = 4 Hz), 2.88 (s, 3 H), 3.81 (AB q, 4 H, $^2J_{HCH}$ = 12 Hz), 4.25 (dd, 1 H, J_{XA} = 8 Hz, J_{XB} = 4 Hz), 7.31 (s, 10 H). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.4; H, 6.2; N, 8.6. Found: C, 70.2; H, 6.3; N, 8.6.

***N*-Cyclohexyl-3-[(*N,N*-dibenzylamino)oxy]pyrrolidine-2,5-dione (7d).** By the procedure used to prepare **7a**, compound **7d** was prepared from 5.3 g (25 mmol) of **6a** and 4.5 g (25 mmol) of **5d** in 50 mL of THF (24 h at reflux temperature). The residue was recrystallized from ethanol to give 6.0 g (61%) of a white solid: mp 75–77 °C; IR ν 1780, 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (80 Mz) δ 1.25 (complex m, 10 H), 1.81 (dd, 1 H, J_{AB} = 15 Hz, J_{AX} = 6 Hz), 2.25 (dd, 1 H, J_{BA} = 15 Hz, J_{BX} = 4 Hz), 3.80 (complex m, 5 H), 4.19 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} = 4 Hz), 7.25 (s, 10 H). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.4; H, 7.2; N, 7.1. Found: C, 73.8; H, 7.1; N, 7.1.

***N*-1-Octadecyl-3-[(*N,N*-dibenzylamino)oxy]pyrrolidine-2,5-dione (7e).** By the procedure used to prepare **7a**, compound **7e** was prepared from 6.1 g (29 mmol) of **6a** and 10.0 g (29 mmol) of **5e** in 50 mL of THF (40 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 9:1, heptane–ethyl acetate eluent) to give 8.0 g (49%) of a waxy solid: IR (CH_2Cl_2) ν 1785, 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (80 MHz) δ 0.89 (t, 3 H), 1.29 (s, 32 H), 1.91 (dd, 1 H, J_{AB} = 16 Hz, J_{AX} = 4 Hz), 2.29 (dd, 1 H, J_{BA} = 16 Hz, J_{BX} = 8 Hz), 3.98 (AB q, 4 H, $^2J_{HCH}$ = 12 Hz), 4.37 (dd, 1 H, J_{XA} = 8 Hz, J_{XB} = 4 Hz), 7.35 (complex m, 10 H). Anal. Calcd for $C_{36}H_{54}N_2O_3$: C, 76.8; H, 9.7; N, 5.0. Found: C, 76.8; H, 9.6; N, 4.8.

***N*-Phenyl-3-[(*N,N*-diethylamino)oxy]pyrrolidine-2,5-dione (7f).** By the procedure used to prepare **7a**, compound **7f** was prepared from 4.5 g (50 mmol) of **6b** and 8.7 g (50 mmol) of **5a** in 50 mL of THF (9.5 h at reflux temperature). The residue was recrystallized from ethanol to give 6.1 g (46%) of an off-white solid: mp 110–112 °C; IR (CH_2Cl_2) ν 1790, 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (80 MHz) δ 1.14 (t, 6 H), 2.97 (complex m, 6 H), 4.89 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} = 8 Hz), 7.33 (complex m, 5 H). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9; N, 10.7. Found: C, 63.9; H, 6.8; N, 10.5.

3-(*N,N*-Dibenzylamino)-1-phenylpyrrolidine-2,5-dione (9). A suspension of 0.9 g (5 mmol) of **5a** and 1.0 g (5 mmol) of *N,N*-dibenzylamine in 15 mL of THF was heated at reflux temperature for 6 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, 3:2, heptane–ethyl acetate eluent) to give 0.3 g (16%) of a white solid: mp 127–130 °C; IR (CH_2Cl_2) ν 1785, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (80 MHz) δ 2.77 (dd, 1 H, J_{AB} = 19 Hz, J_{AX} = 6 Hz), 2.95 (dd, 1 H, J_{BA} = 19 Hz, J_{BX} = 9 Hz), 3.84 (AB q, 4 H, $^2J_{HCH}$ = 14 Hz), 4.11 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} 9 Hz), 7.32 (complex m, 15 H). Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.8; H, 6.0; N, 7.6. Found: C, 77.6; H, 6.2; N, 7.6.

Oxidation of 3-(*N,N*-Dibenzylamino)pyrrolidine-2,5-dione. To a stirred solution of 100 mg (0.27 mmol) of **9** in 5 mL of methylene chloride at −5 °C was added a solution of 55 mg (0.27 mmol) of *m*-chloroperoxybenzoic acid in 4 mL of methylene chloride. The reaction mixture was stirred for 1 h at 0 °C, and then the solvent was removed in vacuo. The crude reaction mixture, which was analyzed by ^1H NMR and TLC (1:1, hep-

(29) (a) Consequently, the N-alkylation product isolated by Winterfeldt is the result of kinetic control, whereupon Cope elimination reaction followed by O-alkylation leads to the product of thermodynamic control. For a review, see: Chandrasekhar, S. *Chem. Soc. Rev.* **1987**, *16*, 313–338. (b) The study of Winterfeldt, of course, involved the reaction of the more electrophilic acetylenedicarboxylate.

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tane–ethyl acetate), was a mixture of **5a**, **6a**, and a small quantity of **9**. No evidence was observed for the presence of **7a**.

1,1-Bis{4-[3-[(*N*,*N*-dibenzylamino)oxy]-2,5-dioxopyrrolidin-1-yl]phenyl}methane (12). By the procedure used to prepare **7a**, compound **12** was prepared from 5.3 g (25 mmol) of **6a** and 4.5 g (12 mmol) of **11** in 50 mL of THF (16 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 7:3, heptane–ethyl acetate eluent) followed by recrystallization from nitromethane to give 6.0 g (61%) of a white solid: mp 141–149 °C; IR (CH_2Cl_2) ν 1790, 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (200 MHz) δ 2.15 (dd, 2 H, J_{AB} = 20 Hz, J_{AX} = 5 Hz), 2.49 (dd, 2 H, J_{BA} = 20 Hz, J_{BX} = 8 Hz), 3.93 (s, 2 H), 4.09 (AB q, 8 H, $^2J_{HCH}$ = 16 Hz), 4.57 (dd, 2 H, J_{XA} = 5 Hz, J_{XB} = 8 Hz), 7.19 (d, 4 H), 7.29 (d, 4 H), 7.43 (complex m, 20 H). Anal. Calcd for $C_{49}H_{44}N_4O_6$: C, 75.0; H, 5.6; N, 7.1. Found: C, 75.1; H, 5.8; N, 7.0.

Reaction of *N*,*N*-Dibenzylhydroxylamine with *N*,*N*-1,2-Phenylenedimaleimide. By the procedure used to prepare **7a**, compound **14a** was prepared from 5.3 g (25 mmol) of **6a** and 3.4 g (12 mmol) of **13a** in 50 mL of THF (72 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 7:3, heptane–ethyl acetate eluent) to give two products. The higher R_f component was isolated to give 5.9 g (71%) of a white solid, **14a**: IR (CH_2Cl_2) ν 1800, 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (200 MHz) δ 2.21 (dd, 2 H, J_{AB} = 19 Hz, J_{AX} = 4 Hz), 2.43 (dd, 2 H, J_{BA} = 19 Hz, J_{BX} = 8 Hz), 3.95 (AB q, 8 H, $^2J_{HCH}$ = 13 Hz), 4.43 (dd, 2 H J_{XA} = 4 Hz, J_{XB} = 8 Hz), 7.39 (complex m, 24 H). Anal. Calcd for $C_{42}H_{38}N_4O_6$: C, 72.6; H, 5.5; N, 8.1. Found: C, 72.6; H, 5.4; N, 7.9. The lower R_f component was isolated to give 0.6 g (10%)[32] of a white solid, **14b**: ^1H NMR ($CDCl_3$) (200 MHz) δ 2.05 (dd, 1 H, J_{AB} = 20 Hz, J_{AX} = 6 Hz), 2.45 (dd, 1 H, J_{BA} = 20 Hz, J_{BX} = 8 Hz), 3.63 (AB q, 4 H, $^2J_{HCH}$ = 12 Hz), 4.43 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} = 8 Hz), 6.77 (s, 2 H), 7.33 (complex m, 14 H). Anal. Calcd for $C_{28}H_{23}N_3O_5$: C, 69.8; H, 4.8; N, 8.7. Found: C, 70.0; H, 5.1; N, 8.5.

Reaction of *N*,*N*-Dibenzylhydroxylamine with *N*,*N*-1,3-Phenylenedimaleimide. By the procedure used to prepare **7a**, compound **14c** was prepared from 5.3 g (25 mmol) of **6a** and 3.4 g (12 mmol) of **13b** in 50 mL of THF (72 h at reflux temperature). The residue was purified by preparative HPLC (silica gel, 7:3, heptane–ethyl acetate eluent) to give two products. The higher R_f component was isolated to give 3.8 g (46%) of a white solid, **14c**: ^1H NMR ($CDCl_3$) (200 MHz) δ 2.09 (dd, 2 H, J_{AB} = 18 Hz, J_{AX} = 4 Hz), 2.43 (dd, 2 H, J_{BA} = 18 Hz, J_{BX} = 8 Hz), 3.67 (AB q, 8 H, $^2J_{HCH}$ = 13 Hz), 4.51 (dd, 2 H, J_{XA} = 4 Hz, J_{XB} = 8 Hz), 7.33 (complex m, 24 H). Anal. Calcd for $C_{42}H_{38}N_4O_6$: C, 72.6; H, 5.5; N, 8.1. Found: C, 72.3; H, 5.4; N, 7.7. The lower R_f component was isolated to give 1.2 g (21%)[32] of a white solid, **14d**: ^1H NMR ($CDCl_3$) (200 MHz) δ 2.05 (dd, 1 H, J_{AB} = 20 Hz, J_{AX} = 6 Hz), 2.39 (dd, 1 H, J_{BA} = 20 Hz, J_{BX} = 8 Hz), 3.97 (AB q, 4 H, $^2J_{HCH}$ = 12 Hz), 4.53 (dd, 1 H, J_{XA} = 6 Hz, J_{XB} = 8 Hz), 6.85 (s, 2 H), 7.27 (complex m, 14 H). Anal. Calcd for $C_{28}H_{23}N_3O_5$: C, 69.8; H, 4.8; N, 8.7. Found: C, 69.5; H, 4.9; N, 8.8.

Kinetic Rate Studies. The progress of the reaction of **5a** (100 mmol) with **6a** (100 mmol) in 16 mL of benzene-d_6 at 65.5 °C (thermally regulated oil bath) was monitored by ^1H NMR spectroscopy (90 MHz) both in the presence and absence of *m*-dinitrobenzene (110 mmol). Toluene (100 mmol) was used as an internal standard.

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Registry No. **5a**, 941-69-5; **5b**, 541-59-3; **5c**, 930-88-1; **5d**, 1631-25-0; **5e**, 17450-30-5; **6a**, 621-07-8; **6b**, 3710-84-7; **7a**, 117022-01-2; **7b**, 117022-02-3; **7c**, 117022-03-4; **7d**, 117022-04-5; **7e**, 117022-05-6; **7f**, 117039-48-2; **8**, 117022-06-7; **9**, 117022-07-8; **10**, 117022-08-9; **11**, 13676-54-5; **12**, 117022-09-0; **13a**, 13118-04-2; **13b**, 3006-93-7; **14a**, 111363-49-6; **14b**, 117022-10-3; **14c**, 117022-11-4; **14d**, 117022-12-5; $(PhCH_2)_2NH$, 103-49-1.

(32) Yield of monoadduct based upon starting maleimide.

Synthesis of 4-Aryl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyrazines

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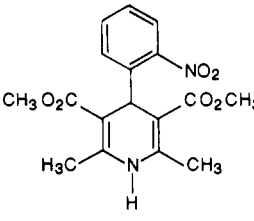
Members of the 4-aryl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines are clinically useful agents for the treatment of cardiovascular diseases such as angina pectoris[2] and hypertension.[3] These compounds exert their spasmolytic and vasodilating activity through their ability to inhibit movement of calcium through certain membrane channels, thus interfering with the calcium dependent processes associated with contraction of vascular smooth muscle.[4,5] Representative of the compounds in this series is nifedipine **1**, which is currently marketed as an antianginal and antihypertensive agent.



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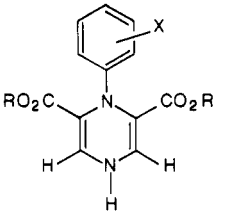

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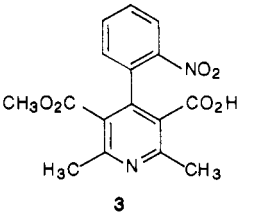

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Our interest in this series centered around the identification of analogues that would possess significant calcium antagonist activity and a longer duration of action than nifedipine and related compounds. One such series was expected to be the 4-aryl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyrazines **2**. Due to the presence of the aryl-substituted nitrogen atom at the 4-position of the heterocyclic ring, oxidative aromatization of this ring should be metabolically less favorable. Metabolism studies of nifedipine indicated that a main metabolite is the biologically inert pyridine acid **3**.[6] Thus, agents resistant to this transformation would be expected to possess more favorable pharmacokinetics and less frequent dosing regimens.

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