$$M^K_{Cu_u} = -1/3$$

$$M^K_{Ni_u} = 4/3 \quad u = x, y, z \quad K = A, B$$

and (13) becomes (11). In the general case, the $\mathbf{M}_i^K$ matrices are not isotropic but have quite a general form. The components of $\mathbf{J}_{AB}$ can then be expressed according to

$$J_{AB_{uv}} = \sum_{KK'} \sum_{lm} \tilde{M}^A_{Ku} (J^{AB}_{KK'}\delta_{lm} + D^{AB}_{KK'_{lm}}) M^B_{K'_{mv}} \quad (14)$$

where $K, K' \equiv$ Cu, Ni, l and m run from 1 to 3, $J^{AB}_{KK'} = {}^1/_3 Tr(\mathbf{J}^{AB}_{KK'})$ and $\mathbf{D}^{AB}_{KK'} = \mathbf{J}^{AB}_{KK'} - J^{AB}_{KK'}\mathbf{I}$ where $\mathbf{I}$ is the identity matrix. From (14), it clearly appears that when the $\mathbf{M}_i^K$ matrices are not isotropic, the isotropic parts of the $\mathbf{J}^{AB}_{KK'}$ dyadics can contribute to the anisotropic components of $\mathbf{J}_{AB}$.

Registry No. Cu(salen)Ni(hfa)$_2$, 71073-29-5; Cu(salen), 14167-15-8; Ni(hfa)$_2$(H$_2$O)$_2$, 98088-59-6.

Supplementary Material Available: Listing of structure factor amplitudes, the thermal parameters for non-hydrogen atoms (Table VI), and the positional and thermal parameters for hydrogen atoms (Table VII) (32 pages). Ordering information is given on any current masthead page.

Combinational *O*-Aryl Carbamate and Benzamide Directed Ortho Metalation Reactions. Synthesis of Ochratoxin A and Ochratoxin B

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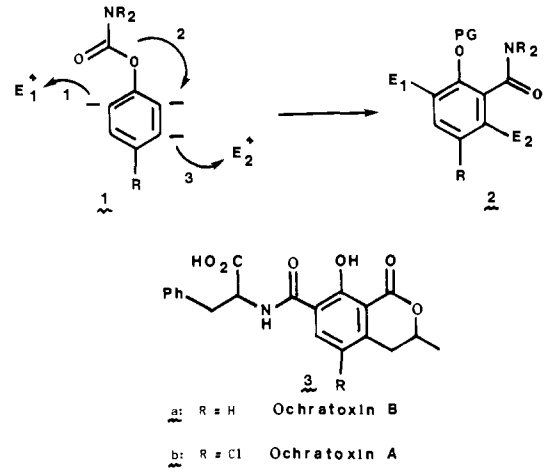
Abstract: The syntheses of isocoumarins **9a** and **9b**, known penultimate precursors for the toxic fungal metabolites ochratoxin B (**3a**) and ochratoxin A (**3b**), respectively, are reported. The syntheses are initiated from *O*-aryl carbamates **4a,b** and proceed through intermediates **5c,d**, **7c,d**, and **8b,c** by a synthetic design that involves comprehensive application of the directed ortho metalation reaction on *O*-aryl carbamates and tertiary benzamides.

Directed metalation-derived ortho-lithiated benzamides,[1] and more recently, the corresponding *O*-aryl carbamates,[2] are becoming recognized as useful synthons for the regioselective construction of diverse polysubstituted aromatics.[3] Herein we report the combinational use of carbamate- and amide-directed ortho metalation reactions to achieve rapid access to multifunctional aromatic systems according to Scheme I.

In this synthetic design, involving comprehensive use of aromatic metalation, the first electrophile (E_1^+) introduced into the ortho-lithiated carbamate **1** (step 1) is chosen to be compatible with subsequent metalation conditions and/or a weaker ortho director than the carbamate.[4] This forces the second metalation into the alternative ortho site, thereby triggering 1,3-carbamoyl rearrangement (step 2).[2] Following phenol protection (PG), the third metalation is directed by the migrated amide, leading to regiospecific E_2^+ introduction (step 3) (especially if R = OMe),[1] thus concluding the construction of a contiguously tetra- or pentasubstituted system (**2**). The utility of this conceptualization is demonstrated in short syntheses of ochratoxin A (**3b**)[5] and ochratoxin B (**3a**),[5] toxic metabolites isolated from strains of *Aspergillus ochraceus* and *Penicillium viridicatum*, which constitute human and animal health hazards owing to their presence in agricultural products.[6-9]

Scheme I

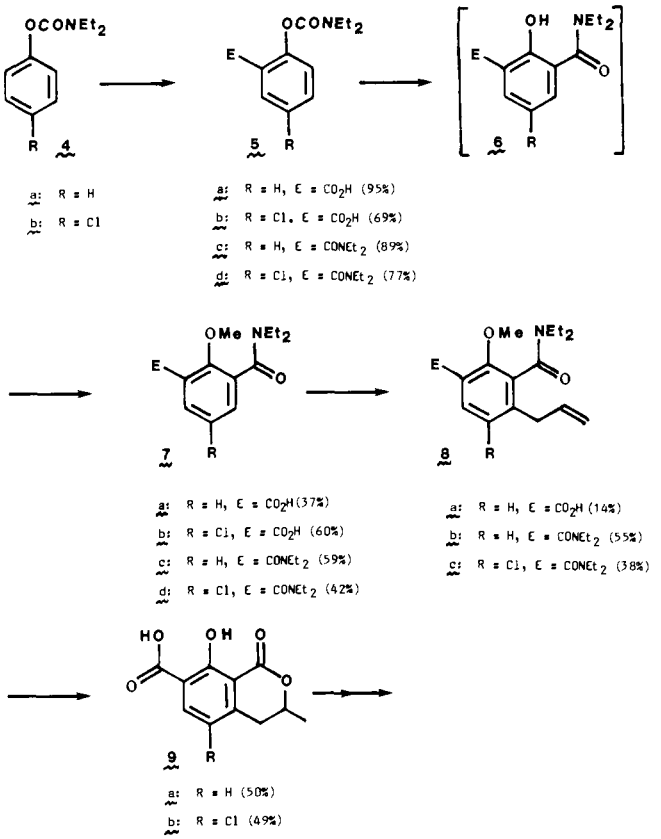


Metalation of the readily accessible *O*-aryl carbamate **4a** with *sec*-BuLi/TMEDA under the widely recognized standard conditions (THF/−78 °C) followed by quenching with carbon dioxide[2] provided the benzoic acid **5a** in excellent yield (Scheme II). Under identical conditions, the chloro carbamate **4b** smoothly afforded compound **5b** in somewhat lower yield. Carbamate O-to-C 1,3-migration in **5a** was effected also under the standard *sec*-BuLi/TMEDA (2 equiv) metalation conditions followed by slow warming to room temperature[2] to give the intermediate phenol **6a**.[10] For convenience in purification, **6a** was methylated, a step that required a subsequent base-catalyzed hydrolysis to reverse the unavoidable formation of the methyl ester. The final product **7a** was thereby obtained in modest yield.[11]

(1) Beak, P.; Snieckus, V. *Acct. Chem. Res.* **1982**, *15*, 306.
(2) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.
(3) For recent methodological and target-oriented endeavors, see: Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95.
(4) Intramolecular competition metalation experiments between carbamate and amide have shown that the former is a somewhat better ortho director: Miah, M. A. J.; Snieckus, V., unpublished results.
(5) Previous syntheses: (a) Steyn, P. S.; Holzapfel, C. W. *Tetrahedron* **1967**, *23*, 4449; (b) Roberts, J. C.; Woollven, P. *J. Chem. Soc. C* **1970**, 278; (c) Kraus, G. A. *J. Org. Chem.* **1981**, *46*, 201.
(6) For other, simply modified ochratoxin metabolites, see: Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Product Chemistry"; Kodansha Ltd. (Tokyo) and Academic Press (New York), 1975; Vol. II, p 198.
(7) Korgh, P. In "Mycotoxins in Human and Animal Health"; Rodricks, J. V., Hesseltine, C. W., Mehlman, M. A., Eds.; Pathotox Publishers: Fark Forest South, IL, 1977; p 489.
(8) Wood, G. M. *Chem. Ind (London)* **1982**, 972.
(9) For biosynthesis, see: Vleggaar, R.; Steyn, P. S. In "The Biosynthesis of Mycotoxins"; Steyn, P. S., Ed.; Academic Press: New York, 1980; p 395.
(10) That the potentially expected ketone formation from the reaction of a benzoic acid with *sec*-BuLi does not constitute a problem has been previously demonstrated; see: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
(11) Attempts at a further abbreviation by forming the *O,O,C* trianion of **6a**, R = H, in situ failed. See also: Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, 4515.

0002-7863/85/1507-6312$01.50/0

Scheme II



Adapting the strategy recently developed for a general synthesis of isocoumarins,[12] **7a** was metalated (2 equiv of *sec*-BuLi/TMEDA) and transmetalated (excess $MgBr_2 \cdot Et_2O$). The presumed intermediate Grignard reagent was treated with allyl bromide to afford **8a** in 14% yield (as its methyl ester). The conversion of **8a** into **9a**, the known relay intermediate for ochratoxin B (**3a**), was readily accomplished under the hydrochloric acid catalyzed conditions previously used for our general isocoumarin synthesis.[12] Isocoumarin **9a** showed physical and spectral properties identical with those reported for previously synthesized material.[5a]

In spite of considerable experimentation, improvement in the yield of the transformation **7a** → **8a** was not achieved. Furthermore, the chloro benzamide **7b** precursor for ochratoxin A, obtained in good yield by an analogous sequence **5b** → **6b** → **7b**, failed to undergo the transmetalation–allylation reaction corresponding to the conversion **7a** → **8a**. In view of these results, we turned our attention to incorporating the $CONEt_2$ group as a base-stable first electrophile (E_1^+ in Scheme I), which would be ultimately convertible by hydrolysis into the 7-carboxylic acid substituent of the ochratoxins.

Metalation of **4a** and **4b** followed by diethylcarbamoyl chloride quench furnished the O-carbamate benzamides **5c** and **5d**, respectively. The 1,3-carbamoyl migration and methylation sequence was carried out as described above to afford, via the unisolated phenols **6c** and **6d**, the isophthalamides **7c** and **7d**, respectively.[13] The syntheses of **7c** and **7d** were abbreviated without great compromise in overall yield by carrying out a one-pot $ClCONEt_2$ quench and carbamate migration sequence on **4a** and **4b**, respectively (see Experimental Section). Ortho lithiation of **7c** and **7d** followed by transmetalation with $MgBr_2$ and treatment with allyl bromide according to our general protocol[12] now succeeded to provide the O-allylated intermediates **8b** and **8c**,[14] respectively. In attempts to improve the yields of these conversions, the metalation of **7c** was studied briefly as a function of time and excess *sec*-BuLi. Increase in metalation time under the standard conditions had a relatively minor effect on anion formation as evidenced from MeOD quench experiments (0.5-h metalation, 87% yield, 38.5% d_1 by mass spectroscopy; 2-h metalation, 74% yield, 49.6% d_1). On the other hand, metalation under the standard conditions but with 2.2 equiv of *sec*-BuLi for 2 h resulted in 80.0% d_1 incorporation although product yield decreased to 61%. Encouraged by the last result, we transmetalated ortho-lithiated **7c** (2.2 equiv of *sec*-BuLi/0.5–2 h) with $MgBr_2$ and allylated the resulting product according to the earlier described procedure. The yields of product **8b** were similar (48–51%) to those obtained in experiments with 1.1 equiv of *sec*-BuLi, thus suggesting that these modest yields are inherent in the transmetalation–allylation process and are not due to the initial ortho lithiation.

In the final step of the synthesis, extended reflux of **8b** and **8c** in 6 N HCl solution effected lactonization, amide hydrolysis, and demethylation in one pot to give the isocoumarin carboxylic acids **9a** and **9b**, respectively. Compounds **9a** and **9b** showed physical and spectral properties identical with those reported in the literature. Since **9a** and **9b** have been previously converted into ochratoxin B (**3a**)[5b] and ochratoxin A (**3b**),[5] respectively, by appropriate peptide coupling with phenylalanine derivatives, this work constitutes total syntheses of both of these toxic metabolites.

In conclusion, the syntheses of isocoumarins **9a** and **9b**, penultimate intermediates for ochratoxin B (**3a**) and ochratoxin A (**3b**), have been completed in four steps and in 14% and 6% overall yields, respectively. These compare favorably with the previously reported yields of 10%,[5a] 1%,[5b] and 20%[5c] for these intermediates. In further compensation, the illustrated strategy (Scheme I) should be adaptable to abbreviated syntheses of analogues of these fungal metabolites and appears to be sufficiently versatile for the preparation of unusually substituted isocoumarins.

Experimental Section[15]

Synthesis of *O*-Aryl Carbamates 4a–b. These compounds were prepared according to a standard literature procedure.[16]

***O*-Phenyl Diethylcarbamate (4a)**: 90% yield; bp 88–90 °C (0.3 mm) (lit.[17] bp 107–108 °C (1 mm)); IR (neat) ν(max) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 6 H, J = 7 Hz), 3.42 (q, 4 H, J = 7 Hz), 7.05–7.39 (m, 5 H); MS m/e 193 (M^+).

***O*-4-Chlorophenyl Diethylcarbamate (4b)**: 95% yield; bp 86–88 °C (0.01 mm) (lit.[18] bp 93–95 °C (0.3 mm)); IR (neat) ν(max) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (t, 6 H, J = 7 Hz), 3.38 (q, 4 H, J = 7 Hz), 7.05 (d, 2 H, J = 9 Hz), 7.32 (d, 2 H, J = 9 Hz); MS m/e 229, 227 (M^+).

General Metalation Procedure. Syntheses of 5a–d. The following procedures are representative for the preparation of compounds **5a–d**.

***O*-2-Carboxyphenyl Diethylcarbamate (5a).** A solution of *O*-phenyl diethylcarbamate (**4a**) (4.7 g, 24.35 mmol) in dry THF (15 mL) was added to a stirred solution of *sec*-BuLi (22 mL, 26.8 mmol, 1.22 M solution) and TMEDA (4.0 mL, 26.8 mmol) in THF (250 mL) under N_2 and maintained at −78 °C. After 1 h, dry CO_2 was passed through the reaction mixture for 2 h and the stirred reaction mixture was allowed to attain room temperature overnight. The reaction mixture was treated with saturated NH_4Cl solution (25 mL) and the whole was evaporated to dryness in vacuo. The remaining residue was extracted with Et_2O (3 × 25 mL), and the aqueous layer was acidified with 2 N HCl (pH ≈3) and extracted with Et_2O (3 × 25 mL). The ethereal layer was washed, dried (Na_2SO_4), and evaporated to yield **5a** as a thick oil (5.49 g, 95%); IR ($CHCl_3$) ν(max) 1712 cm^{-1}; NMR ($CDCl_3$) δ 1.12–1.36 (m, 6 H), 3.26–3.75 (m, 4 H), 7.11–7.69 (m, 3 H), 7.98–8.09 (m, 2 H, 1 H exchangeable with D_2O); MS m/e 237.0993 (M^+) (calcd for $C_{12}H_{15}NO_4$ 237.1001).

***O*-2-Carboxy-4-chlorophenyl Diethylcarbamate (5b).** Compound **5b** was prepared in 69% yield from *O*-4-chlorophenyl diethylcarbamate (**4b**) by the procedure described for **5a**: mp 101–102 °C (PhH–hexane); IR

(12) Sibi, M. P.; Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737.

(13) The value of this approach is evident from the failure to obtain **6c** directly from *N,N*-diethylisophthalamide by the $B(OMe)_3/H_2O_2$/HOAc method (see footnote 22 in: Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531).

(14) *N,N*-Diethyl-3-chlorobenzamide undergoes metalation at the site common to the two directing groups. See ref 10.

(15) For general methods, see ref 12.

(16) Lustig, E.; Benson, W. R.; Duy, N. *J. Org. Chem.* **1967**, *32*, 851.

(17) Isakova, A. P.; Naumov, Yu. A.; Nikeryasova, S. V.; Stepanova, A. A. *Zh. Org. Khim.* **1982**, *18*, 1287; *Chem. Abstr.* **1982**, *97*, 109661.

(18) Societé des Usines Chimiques Rhône-Poulenc British Patent 753766; *Chem. Abstr.* **1957**, *51*, 4640.

($CHCl_3$) ν(max) 1710, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.11–1.35 (m, 6 H), 3.25–3.60 (m, 4 H), 5.46 (br, 1 H, exchangeable with D_2O), 7.12 (d, 1 H, J = 8.6 Hz), 7.53 (dd, 1 H, J = 8.6, 2.7 Hz), 8.00 (d, 1 H, J = 2.3 Hz); MS m/e 273, 271 (M^+). Anal. Calcd for $C_{12}H_{14}NO_4Cl$: C, 53.04; H, 5.19; N, 5.15; Cl, 13.05. Found: C, 53.21; H, 5.41; N, 5.45; Cl, 12.82.

O-2-(Diethylcarbamoyl)phenyl Diethylcarbamate (5c). A solution of *O*-phenyl diethylcarbamate (**4a**) (4.023 g, 20.84 mmol) in THF (20 mL) was added to a stirred solution of *sec*-BuLi (19.1 mL, 22.93 mmol, 1.20 M solution) and TMEDA (3.45 mL, 22.93 mmol) in THF (200 mL) under N_2 maintained at −78 °C. After 1 h, the stirred reaction mixture was quenched with diethylcarbamoyl chloride (2.8 mL, 22.93 mmol) and allowed to attain room temperature overnight. Standard workup followed by chromatography over silica gel (20% EtOAc–hexane eluent) gave **5c** (5.41 g, 89%). Distillation provided a pure sample: bp 158–160 °C (0.4 mm) (lit.[17] 180–185 °C (1 mm)); IR ($CHCl_3$) ν(max) 1711, 1622 cm^{-1}; NMR (acetone-d_6) δ 0.96–1.27 (m, 12 H), 3.07–3.64 (m, 8 H), 7.19–7.50 (m, 4 H); MS m/e 292 (M^+).

O-2-(Diethylcarbamoyl)-4-chlorophenyl Diethylcarbamate (5d). Compound **5d** was prepared in 77% yield from *O*-4-chlorophenyl diethylcarbamate (**4b**) according to the procedure described for **5c**: bp 140–150 °C (0.8 mm); IR ($CHCl_3$) ν(max) 1716, 1626 cm^{-1}; NMR ($CDCl_3$) δ 0.98–1.29 (m, 12 H), 3.07–3.65 (m, 8 H), 7.11–7.42 (m, 3 H); MS m/e 328, 326 (M^+). Anal. Calcd for $C_{16}H_{23}N_2O_3Cl$: C, 58.80; H, 7.09; N, 8.57. Found: C, 58.93; H, 7.10; N, 8.43.

General Carbamoyl Migration Procedure. Synthesis of 7a–d. The following procedure is representative for the preparation of **7a–d**.

***N,N*-Diethyl-2-methoxy-3-carboxybenzamide (7a).** A solution of *O*-2-carboxyphenyl diethylcarbamate (**5a**) (2.063 g, 8.70 mmol) in dry THF (10 mL) was added to a stirred solution of *sec*-BuLi (13.8 mL, 19.14 mmol, 1.39 M solution) and TMEDA (2.9 mL, 19.14 mmol) in THF (170 mL) maintained at −78 °C under N_2. The stirred reaction mixture was allowed to attain room temperature overnight and treated with a saturated NH_4Cl solution. The organic solvent was removed in vacuo and the remaining solution was extracted with Et_2O (3 × 25 mL). The aqueous layer was acidified with 2 N HCl (pH 3), and the whole was extracted with Et_2O–CH_2Cl_2 (1:1, 3 × 25 mL) and worked up in the usual way to give 1.7 g of a solid that was refluxed with a mixture of MeI (10 mL) and K_2CO_3 (3 g) in acetone (30 mL) for 20 h. Standard workup followed by silica gel chromatography (1:1 EtOAc–hexane eluent) furnished 0.976 g (42%) of *N,N*-diethyl-2-methoxy-3-(methoxycarbonyl)benzamide as an oil: IR ($CHCl_3$) ν(max) 1725, 1618 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7 Hz), 1.26 (t, 3 H, J = 7 Hz), 3.01–3.36 (m, 4 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 7.18 (t, 1 H, J = 7.4 Hz), 7.41 (dd, 1 H, J = 7.4 Hz), 7.84 (dd, 1 H, J = 7.4, 2.1 Hz).

This ester (1 g, 3.77 mmol) was refluxed with NaOH (3 g) in a mixture of MeOH (60 mL) and water (10 mL) for 24 h. The methanol was removed in vacuo and the remaining aqueous solution was extracted with Et_2O (2 × 30 mL). The aqueous layer was acidified with concentrated HCl, saturated with NH_4Cl, and extracted with CH_2Cl_2 (5 × 30 mL). Standard workup gave crude solid material that upon recrystallization from CH_2Cl_2–hexane gave 0.84 g (89%) of **7a**: mp 123–125 °C; IR (KBr) ν(max) 3400, 1701, 1586 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7 Hz), 1.29 (t, 3 H, J = 7 Hz), 3.17 (q, 2 H, J = 7 Hz), 3.40–3.80 (br, 2 H), 4.05 (s, 3 H), 7.30 (t, 1 H, J = 7.4 Hz), 7.50 (dd, 1 H, J = 7.4, 1.9 Hz), 8.17 (dd, 1 H, J = 7.4, 1.9 Hz); MS m/e 251 (M^+). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.57. Found: C, 62.30; H, 6.75; N, 5.54.

***N,N*-Diethyl-2-methoxy-3-carboxy-5-chlorobenzamide (7b).** Compound **7b** was obtained in 60% yield via its corresponding methyl ester from **5b** according to the procedure described for the preparation of **7a**. **7b**: mp 101–102 °C (Et_2O–hexane); IR (KBr) ν(max) 1722, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.00–1.36 (m, 6 H), 3.04–3.51 (m, 4 H), 4.01 (s, 3 H), 7.44 (d, 1 H, J = 2.7 Hz), 8.09 (d, 1 H, J = 2.7 Hz); MS m/e 287, 285 (M^+). Anal. Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.31; H, 5.67; N, 4.84; Cl, 12.64.

***N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)benzamide (7c).** Compound **7c** was obtained in 59% yield from **5c** following the procedure used for the preparation of **7a**. **7c**: mp 82 °C (Et_2O–hexane); IR ($CHCl_3$) ν(max) 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (t, 6 H, J = 7.1 Hz), 1.26 (t, 6 H, J = 7.3 Hz), 3.05–3.80 (m, 8 H), 3.85 (s, 3 H), 7.19–7.22 (m, 3 H); MS m/e 306 (M^+). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.63; H, 8.55; N, 9.14. Found: C, 66.82; H, 8.62; N, 8.83.

***N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)-5-chlorobenzamide (7d).** Compound **7d** was obtained in 42% yield from **5d** according to the procedure given for the preparation of **7a**. **7d**: mp 85–87 °C (hexane); IR ($CHCl_3$) ν(max) 1629 cm^{-1}; NMR ($CDCl_3$) δ 0.98–1.33 (m, 12 H), 3.14–3.70 (m, 8 H), 3.82 (s, 3 H), 7.20 (s, 1 H); MS m/e 342, 340 (M^+). Anal. Calcd for $C_{17}H_{25}N_2O_3Cl$: C, 59.91; H, 7.39; N, 8.22; Cl, 10.40. Found: C, 59.70; H, 7.44; N, 8.17; Cl, 10.69.

One-Pot Procedure for the Preparation of 7c. Compound **4a** (1.87 g, 9.69 mmol) was added to a stirred mixture of *sec*-BuLi (10.3 mL, 10.7 mmol, 1.04 M) and TMEDA (1.6 mL, 10.7 mmol) in THF (150 mL) maintained at −78 °C under N_2. After 1 h, the mixture was quenched with diethylcarbamoyl chloride (1.3 mL, 10.7 mol) and allowed to attain room temperature overnight. The reaction mixture was cooled to −78 °C and treated with TMEDA (1.6 mL, 10.7 mmol) and *sec*-BuLi (10.3 mL, 10.7 mmol, 1.04 M) and the whole mixture was allowed to attain room temperature overnight. Standard workup gave an oil (3.5 g) that was refluxed with excess MeI (10 mL) and anhydrous K_2CO_3 (2 g) in acetone (20 mL) solution for 20 h. Normal workup gave an oil (2.58 g) that upon silica gel chromatography (80% Et_2O–hexane eluent) gave **7c** (1.50 g, 50.5%), whose ^1H NMR was identical with that of a sample prepared as described above.

Compound 7d. By a similar procedure to that described for the preparation of **7c**, **4b** was converted in 26% yield into **7d**, whose identity was established by direct comparison with material prepared as described above.

Synthesis of Allylated Benzamides, 8a–c. *N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)-6-allylbenzamide (8b). A solution of *N,N*-diethyl-2-methoxy-3-(diethylcarbamoyl)benzamide (**7c**) (330 mg, 1.08 mmol) in THF (3 mL) was added to a stirred solution of *sec*-BuLi (1.0 mL, 1.19 mmol, 1.24 M solution) and TMEDA (0.18 mL, 1.186 mmol) in THF (75 mL) maintained at −78 °C under N_2. After 30 min, $MgBr_2$·Et_2O (1.35 mL, 3.56 mmol) was added, the mixture was stirred for 45 min and treated with allyl bromide (0.28 mL, 3.23 mmol), and the whole was allowed to warm to room temperature overnight. Standard workup gave a viscous oil (358 mg) that upon preparative TLC (EtOAc eluent) afforded starting material (69 mg) and product **8b** (201 mg, 55%). Kugelrohr distillation provided pure **8b** as a colorless oil: bp 95–105 °C (0.05 mm); IR ($CHCl_3$) ν(max) 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.98–1.37 (m, 12 H), 3.01–3.74 (m, 10 H), 3.84 (s, 3 H), 5.02–5.23 (m, 2 H), 5.7–6.2 (m, 1 H), 7.03 (d, 1 H, J = 7.9 Hz), 7.20 (d, 1 H, J = 7.9 Hz); MS m/e 346 (M^+). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.34; H, 8.73; N, 8.09. Found: C, 69.13; H, 8.90; N, 7.92.

***N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)-5-chloro-6-allylbenzamide (8c).** By the procedure described for the preparation of **8b**, *N,N*-diethyl-2-methoxy-3-(diethylcarbamoyl)-5-chlorobenzamide (**7d**) (505 mg, 1.48 mmol) in THF (3 mL) was sequentially treated with *sec*-BuLi (1.4 mL, 1.63 mmol, 1.18 M solution) and TMEDA (0.24 mL, 1.63 mmol) in THF (70 mL), $MgBr_2$·Et_2O (1.9 mL, 4.9 mmol), and allyl bromide (0.38 mL, 4.44 mmol). Standard workup gave an oil (560 mg) that upon silica gel chromatography (40% Et_2O–hexane eluent) afforded an oil that solidified (213 mg, 38%). Recrystallization from hexane gave colorless crystals of **8c**: mp 72–75 °C; IR ($CHCl_3$) ν(max) 1630 cm^{-1}; NMR (acetone-d_6) δ 0.95–1.38 (m, 12 H), 3.0–3.65 (m, 10 H), 3.79 (s, 3 H), 4.95–5.22 (m, 2 H), 5.65–6.15 (m, 1 H), 7.28 (s, 1 H); MS m/e 383, 381 (M^+). Anal. Calcd for $C_{20}H_{29}N_2O_3Cl$: C, 63.06; H, 7.67; N, 7.35. Found: C, 62.87; H, 7.45; N, 7.24.

***N,N*-Diethyl-2-methoxy-3-carboxy-6-allylbenzamide (8a).** Compound **8a** was prepared according to the procedure described for the preparation of **8b**. Crude **8a** showed a ^1H NMR spectrum consistent with its structure and, for characterization, was converted (MeI/Na_2CO_3/acetone) into its methyl ester: 14% overall yield; bp 95–100 °C (0.05 mm); IR ($CHCl_3$) ν(max) 1725, 1623 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (t, 3 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz), 3.09 (q, 2 H, J = 7 Hz), 3.31–3.82 (m, 4 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.99–5.20 (m, 2 H), 5.68–6.20 (m, 1 H), 7.07 (d, 1 H, J = 8 Hz), 7.80 (d, 1 H, J = 8 Hz); MS m/e 305 (M^+). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.85; H, 7.59; N, 4.59. Found: C, 66.57; H, 7.54; N, 5.10.

Deuteration of *N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)benzamide (7c). Compound **7c** (340 mg, 1.11 mmol) was treated with *sec*-BuLi (1.0 mL, 1.22 mmol, 1.20 M) and TMEDA (0.18 mL, 1.22 mmol) in THF (40 mL) at −78 °C. After stirring for 0.5 h, the reaction mixture was quenched with excess MeOD (0.5 mL, 12.2 mmol) and allowed to attain ambient temperature overnight. Standard workup followed by silica gel chromatography (Et_2O eluent) gave **7c** as an oil (296 mg, 87%). Crystallization from Et_2O–hexane gave colorless crystals: mp 80 °C; MS m/e (relative intensity) 308 (4.85), 307 (16.16), 306 (23.64), 305 (23.23), 277 (4.04), 276 (10.51), 275 (12.73). Calculation for M^+ showed that the product contained 14.8% d_2, 38.5% d_1, and 46.7% d_0.

When **7c** was lithiated under the above identical conditions except for 2 h and quenched with excess MeOD, the product (74% yield) showed for M^+, 13.6% d_2, 49.6% d_1, and 36.8% d_0. When **7c** was lithiated under the same conditions except with 2.2 equiv of *sec*-BuLi for 2 h and likewise quenched, the product (61% yield) showed for M^+ 13.5% d_2, 80.0% d_1, and 6.5% d_0.

Syntheses of Isocoumarins 9a and 9b. 3-Methyl-7-carboxy-8-hydroxyisocoumarin (9a). From 8a. *N,N*-Diethyl-2-methoxy-3-carboxy-6-allylbenzamide (**8a**) (136 mg, 0.47 mmol) was refluxed in 6

N HCl (5 mL) for 24 h. The reaction mixture was diluted with water and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extract was dried (Na_2SO_4) and evaporated to dryness to yield 80 mg (85%) of **9a**, mp 234–236 °C, which was shown to be identical with material obtained below.

From 8b. Compound **8b** (150 mg, 0.43 mmol) was refluxed in 6 N HCl (2 mL) for 4 days. The separated solid was collected by filtration, washed with water, and dried. Recrystallization from acetone gave 45 mg (50%) of **9a** as colorless crystals: mp 234–236 °C (lit.[5a] mp 223 °C); IR (KBr) ν(max) 3490 (br), 1678 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.40 (d, 3 H, J = 6.65 Hz), 2.8–3.2 (m, 2 H), 3.5 (br, 2 H), 4.63–4.76 (m, 1 H), 6.85 (d, 1 H, J = 8 Hz), 7.95 (d, 1 H, J = 8 Hz); ^{13}C NMR (Me_2SO-d_6) δ 20.2, 34.4, 74.7, 110.8, 115.7, 117.7, 136.4, 146.7, 161.8, 165.3, 168.8.

3-Methyl-5-chloro-7-carboxy-8-hydroxyisocoumarin (9b). *N,N*-Diethyl-2-methoxy-3-(diethylcarbamoyl)-5-chloro-6-allylbenzamide (**8c**) (155 mg, 0.41 mmol) was refluxed in 6 N HCl (2 mL) for 4 days. Workup as for **9a** followed by crystallization (acetone–methanol) furnished 51 mg (49%) of **9b** as colorless crystals: mp 246 °C (lit.[5a] mp 229 °C, lit.[5b] mp 246–249 °C dec, lit.[5c] 246 °C); IR (KBr) ν(max) 3288, 1736, 1705, 1667 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.43 (d, 3 H, J = 6.2 Hz), 2.49–3.23 (m, 2 H), 4.70–4.79 (m, 1 H), 7.98 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 20.1, 32.1, 74.4, 112.4, 117.7, 120.6, 136.0, 143.4, 160.2, 165.4, 167.1.

The ^1H and ^{13}C NMR spectra were found to be identical with those reported[5c] for **9b**. Its ^{13}C spectrum was directly compared with that kindly provided by Professor G. A. Kraus.

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Cycloalkylmethyl Radicals. 2. Axial and Equatorial Cyclohexylmethyl and (4-Alkylcyclohexyl)methyl Radicals. First Determination of the Conformational Free Energy Difference of the CH_2· Group[1]

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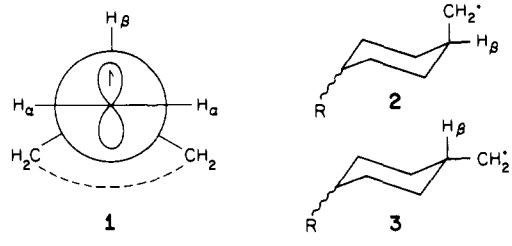
Abstract: At 140 K the EPR spectra of cyclohexylmethyl and (4-alkylcyclohexyl)methyl radicals in which the CH_2· group adopts the axial conformation have $a^{H_\beta} \sim 42$–43 G, while those in which the CH_2· group adopts the equatorial conformation have a^{H_β} = 30–31 G. Both conformers can be observed over a range of temperatures for cyclohexylmethyl and for (*cis*-4-methylcyclohexyl)methyl. For the former radical, the relative conformer concentrations under conditions where ring inversion is rapid relative to radical lifetime can be described by log ([axial]/[equatorial]) = 0.79 − 1.79/θ (where $\theta = 2.3RT$ kcal/mol). At 300 K, therefore, the conformational free energy difference of the CH_2· group in the axial and equatorial positions is $-\Delta G°$ = 0.71 kcal/mol. The greater a^{H_β} value for the axial conformers is attributed to a higher barrier to rotation about the C_α–C_β bond.

We recently reported[4] that two conformers of the cycloundecylmethyl radical, $\overline{CH_2(CH_2)_9CHCH_2}$·, could be detected by EPR spectroscopy at temperatures below 230 K.[5] The main spectroscopic difference between the two conformers lay in the magnitudes of their β-H hyperfine splittings[6] (hfs); at 140 K one conformer had a^{H_β} = 31.1 G and the other had a^{H_β} = 38.3 G. The absolute magnitudes of these two β-H hfs,[7] as well as the fact that for both radicals a^{H_β} decreased with an increase in temperature, indicated that both of these radicals adopted an eclipsed conformation, **1**. It therefore seemed likely that in one conformer the CH_2· group was quasi-axial and in the other it was quasi-equatorial. This suggested to us that axial cyclohexylmethyl radicals, i.e., those with the CH_2· group axial, **2**, and equatorial cyclohexylmethyl radicals, i.e., those with the CH_2· group equatorial, **3**, should be distinguishable by EPR spectroscopy. Such is the case and have been able to make the first measurement of the conformational free energy difference ($-\Delta G°$ value)[8,9] of the CH_2· group in the axial and equatorial conformations.



Results and Discussion

Initial experiments were designed to see whether or not axial, **2**, and equatorial, **3**, CH_2· groups could be unequivocally identified by their β-H hfs. Radicals were generated by bromine atom abstraction from the corresponding cyclohexylmethyl bromides with use of triethylsilyl radicals (formed by photolysis of di-*tert*-butyl peroxide in the presence of triethylsilane).[4] The radicals generated and their β-H hfs at 140 K are listed in Table I.

(*cis*-4-*tert*-Butylcyclohexyl)methyl bromide gave a single radical (a^{H_β} = 41.9 G) which must have CH_2· axial, **2a**. (*trans*-4-*tert*-

(1) Issued as N.R.C.C. No. 24876. For part 1 see ref 4.
(2) N.R.C.C.
(3) St. Andrews.
(4) Kemball, M. L.; Walton, J. C.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1017–1023.
(5) Above this temperature the lines due to the two radicals coalesce to give a single spectrum with a^{H_β} = 29.8 G at 270 K.
(6) Throughout this article β-H refers to the tertiary H adjacent to the CH_2· group.
(7) The two conformers were referred to as cyclohexylmethyl-like and cyclooctylmethyl-like because their β-H hfs' resemble those of the named radicals, viz.[4] 30.4 and 40.1 G, respectively, at 140 K.
(8) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1965.
(9) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.

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