(*Z*)-**15**: IR (neat) 1595, 1492, 1452, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H), 6.44 (dd, J = 11.0, 11.1 Hz, 1 H), 6.36 (d, J = 11.0 Hz, 1 H), 6.32 (d, J = 11.1 Hz, 1 H), 1.82 (s, 6 H).

(*E*)-**16**: IR (neat) 964 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.17 (dd, J = 10.6, 15.0 Hz, 1 H), 5.77 (d, J = 10.6 Hz, 1 H), 5.60 (d, J = 15.0 Hz, 1 H), 1.74 (s, 6 H), 1.04 (s, 9 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 143.3, 132.9, 127.0, 125.5, 33.2, 29.9, 26.0, 18.3; mass spectrum, m/e 138.1 (P).

(*Z*)-**16**: IR (neat) 734 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.21 (dd, J = 11.4, 11.9 Hz, 1 H), 5.91 (d, J = 11.9 Hz, 1 H), 5.27 (d, J = 11.4 Hz, 1 H), 1.80 (s, 3 H), 1.72 (s, 3 H), 1.16 (s, 9 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 139.2, 135.1, 123.2, 121.4, 33.5, 31.5, 26.6, 17.6. Anal. ($C_{10}H_{18}$) C, H.

(*E*)-**17**: IR (neat) 958 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, J = 10.8, 15.2 Hz, 1 H), 5.78 (d, J = 10.8 Hz, 1 H), 5.51 (dd, J = 15.2, 6.9 Hz, 1 H), 2.00 (br m, 1 H), 1.78–1.60 (br, 4 H), 1.74 (s, 6 H), 1.40–1.00 (br, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 138.0, 132.8, 125.5, 124.2, 41.1, 33.3, 26.3, 26.2, 18.2. Anal. ($C_{12}H_{20}$) C, H for the mixture of (*E*)- and (*Z*)-**17**.

(*Z*)-**17**: IR (neat) 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10–6.01 (m, 2 H), 5.17 (m, 1 H), 2.43 (br m, 1 H), 1.81 (s, 6 H), 1.78–1.60 (br, 4 H), 1.40–1.00 (br, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 135.7, 134.9, 122.9, 120.7, 36.6, 33.5, 26.1, 26.0, 18.1.

18: see ref 4 and 17.

(*E*)-**19**: IR (neat) 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (dd, J = 10.7, 15.4 Hz, 1 H), 5.80 (d, J = 10.7 Hz, 1 H), 5.63 (d, J = 15.4 Hz, 1 H), 5.10 (br m, 1 H), 2.18–1.95 (br m, 4 H), 1.76 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.03 (s, 9 H). Anal. ($C_{15}H_{26}$) C, H for the mixture of (*E*)- and (*Z*)-**19**.

(*Z*)-**19**: IR (neat) 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, J = 11.8 Hz, 1 H), 6.01 (dd, J = 11.8, 11.9 Hz, 1 H), 5.31 (d, J = 11.8 Hz, 1 H), 5.10 (br m, 1 H), 1.72 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.16 (s, 9 H).

(*E*)-**20**: IR (neat) 961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (dd, J = 10.7, 15.2 Hz, 1 H), 5.79 (d, J = 10.7 Hz, 1 H), 5.54 (dd, J = 7.1, 15.2 Hz, 1 H), 5.10 (br m, 1 H), 2.27 (br m, 1 H), 2.20–1.94 (br m, 4 H), 1.74 (s, 3 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.40–1.12 (br m, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 138.5, 136.5, 131.5, 125.0, 124.3, 124.2, 41.2, 40.0, 33.3, 26.8, 26.3, 26.2, 25.7, 17.7, 16.7. Anal. ($C_{17}H_{28}$) C, H for the mixture of (*E*)- and (*Z*)-**20**.

(*Z*)-**20**: IR (neat) 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (m, 1 H), 6.08 (d, J = 5.4 Hz, 1 H), 5.19 (br m, 1 H), 5.10 (br m, 1 H), 2.40 (br m, 1 H), 1.78–1.55 (br, 4 H), 1.75 (s, 3 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.40–1.12 (br m, 6 H).

(*E*)-**21**: IR (neat) 961 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.49–7.00 (br m, 5 H), 6.87 (d, J = 15.8 Hz, 1 H), 6.49 (d, J = 15.8 Hz, 1 H), 5.09 (br, 2 H), 1.96 (s, 3 H). Anal. ($C_{11}H_{12}$) C, H for the mixture of (*E*)- and (*Z*)-**21**.

(*Z*)-**21**: IR (neat) 729 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.49–7.00 (br m, 5 H), 6.40 (d, J = 12.3 Hz, 1 H), 6.11 (d, J = 12.3 Hz, 1 H), 4.98 (br, 2 H), 1.70 (s, 3 H).

(*E*)-**22**: IR (neat) 1605, 1495, 1454, 964, 908 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.19 (d, J = 15.8 Hz, 1 H), 5.66 (dt, J = 15.8, 6.1 Hz, 1 H), 4.86 (br, 2 H), 2.87–2.56 (br m, 2 H), 2.56–2.21 (br m, 2 H), 1.82 (s, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 142.2, 141.9, 133.5, 129.9, 128.5, 128.4, 125.9, 114.6. Anal. ($C_{13}H_{16}$) C, H for the mixture of (*E*)- and (*Z*)-**22**.

(*Z*)-**22**: ^1H NMR (90 MHz, $CDCl_3$) δ 5.86 (d, J = 11.6 Hz, 1 H), 5.41 (dt, J = 11.6, 6.4 Hz, 1 H), 4.80 (br, 2 H) for the olefin protons.

(*E*)-**23**: IR (neat) 967, 909 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.11 (d, J = 15.8 Hz, 1 H), 5.57 (dd, J = 15.8, 6.6 Hz, 1 H), 4.86 (br, 2 H), 2.23–1.91 (br m, 1 H), 1.91–1.43 (br, 4 H), 1.82 (s, 3 H), 1.43–1.00 (br, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 142.4, 136.7, 130.3, 114.2, 40.9, 33.1, 26.3, 26.1, 18.7. Anal. ($C_{11}H_{18}$) C, H.

(*Z*)-**23**: ^1H NMR (90 MHz, $CDCl_3$) δ 5.74 (d, J = 11.5 Hz, 1 H), 5.20 (dd, J = 11.5, 9.7 Hz, 1 H), 4.93 (br, 3 H) for the olefin protons.

24: IR (neat) 853 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.77 (br, 1 H), 5.43 (br, 1 H), 2.67–2.20 (br, 6 H), 2.20–1.99 (br, 2 H), 1.99–1.74 (m, 2 H), 1.71–1.37 (br, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 141.8, 141.7, 129.4, 119.0, 38.2, 35.5, 32.1, 30.2, 28.9, 28.1, 26.8, 24.2. Anal. ($C_{12}H_{18}$) C, H.

(*E*)- **and** (*Z*)-**25**: IR (neat) 1600, 1493, 1442 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.49–7.00 (m, 5 H), 6.37 (br, 1 H) [6.23 (br, 1 H) for (*Z*)-**25**], 5.63 (br, 1 H) [5.43 (br, 1 H) for (*Z*)-**25**], 2.81–2.49 (br, 2 H), 2.49–2.16 (br, 2 H), 2.23 (s, 3 H) [2.06 (s, 3 H) for (*Z*)-**25**], 2.11–1.80 (m, 2 H). Anal. ($C_{14}H_{16}$) for the mixture of (*E*)- and (*Z*)-**25**.

(*E*)-**28**: IR (neat) 1604, 1496, 1454, 963 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.20 (br, 5 H), 6.06 (d, J = 15.8 Hz, 1 H), 5.63 (br, 1 H), 5.51 (dt, J = 15.8, 5.1 Hz, 1 H), 2.86–2.54 (br m, 2 H), 2.54–2.26 (br m, 2 H), 2.26–1.91 (br, 4 H), 1.83–1.40 (br, 4 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 142.2, 135.7, 134.1, 128.5, 128.3, 127.6, 125.9, 125.7, 36.4, 34.8, 25.9, 24.8, 22.8, 22.7. Anal. ($C_{16}H_{20}$) C, H.

(*E*)-**29**: IR (neat) 1604, 1495, 1453, 965 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.20 (br, 5 H), 6.06 (d, J = 15.4 Hz, 1 H), 5.77 (t, J = 6.6 Hz, 1 H), 5.57 (dt, J = 15.4, 6.6 Hz, 1 H), 2.89–2.57 (br m, 2 H), 2.57–2.00 (br m, 6 H), 1.91–1.29 (br m, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 142.9, 142.2, 134.8, 132.1, 128.5, 128.3, 125.9, 125.6, 36.4, 34.9, 32.3, 28.6, 27.6, 27.0, 26.4. Anal. ($C_{17}H_{22}$) C, H.

(17) Inoue, Y.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1279–1280.

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Transmetalation and Reverse Transmetalation on Ortho-Activated Aromatic Compounds: A Direct Route to *o,o'*-Disubstituted Benzenes

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Mercury substitution ortho to appropriately activated benzenes was achieved by using the reagent lithium tetramethylpiperidide (LiTMP)/mercuric chloride. LiTMP provides for lithiation ortho to the activating group; $HgCl_2$ functions as an in situ trap effecting mercury-for-lithium transmetalation. Ortho,ortho'-dimercuration was also observed; this occurs by iteration of the transmetalation process. The effects of major variables on these reactions were studied by using primarily *N,N*-diethylbenzamide as the activated substrate. Isopropyl benzoate, 2-phenyl-4,4-dimethyloxazoline, etc. were found to behave similarly. The mercurated aromatics could be converted to the corresponding haloaromatics in excellent yield, providing, for example, a good synthesis of *o,o'*-diiodo-*N,N*-diethylbenzamide, otherwise difficultly accessible. Reverse transmetalation methodology was employed to prepare *o,o'*-dilithiated-*N,N*-diethylbenzamide, which was characterized by its reactions with electrophiles.

Amide activation for ortho-lithiation of aromatic compounds is very well-known.[1] Recently we showed that this phenomenon also occurs on strained systems like cubane and cyclopropane which use orbitals high in s character

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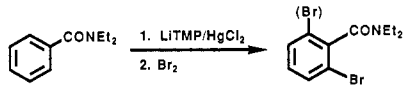
Table I. Metalation/Bromination of *N,N*-Diethylbenzamide

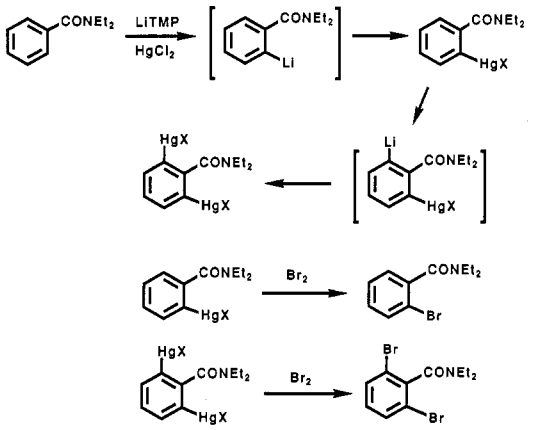


entry	molar ratio amide/LiTMP/$HgCl_2$	reactn time, min	reactn temp, °C	% yield (calibrated GLC) recovered amide	*o*-bromo amide	*o,o'*-dibromo amide
1	1:2.1:1.0	20	0	6	93	2
2	1:1.9:1.0	20	0	88		
3	1:6.0:2.0	20	0		37	45
4	1:8.0:2.0	20	0		16	47
5	1:2.4:1.0	20	0		68	13
6	1:2.4:1.0	120	0		44	30
7	1:2.0:0.50	20	0	7	71	6
8	1:2.0:0.75	20	0		72	17
9	1:6.3:3.0	165	0			51
10	1:6.2:3.0	60	20			64

to bond substituents.[2,3] In these "saturatated" systems the activation is fairly weak and special procedures are necessary to make practical use of it. To this end we developed a transmetalation approach: a strong lithium base is used to generate the ortho-anion in its small equilibrium concentration and an in situ metalloid trap is employed to pull the equilibrium formation of the anion "to the right". Various reagents work:[2-5] a mixture of lithium tetramethylpiperidide (LiTMP) and mercuric chloride has proved to be best in the cases of principal interest to us. In this paper we show briefly how LiTMP/$HgCl_2$ and processes developed for the profitable use of this reagent in the cubane series can be employed productively with aromatic compounds.

We have found that reactions of *N,N*-diethylbenzamide and other activated benzenes with LiTMP/$HgCl_2$ produce the corresponding mono- and dimercury ortho-substituted derivatives. These processes proceed by way of singly ortho-lithiated intermediates and their subsequent mercuration (transmetalation) as shown in Scheme I. The mercurated aromatic compounds can be isolated (e.g., as their chlorides), but their purification is not easy, and their characterization is confused by oligomerization problems and NMR spectra complicated by H–Hg couplings (^{199}Hg, 17% abundance, $I = {}^1/_2$; ^{201}Hg, 13% abundance, $I = {}^3/_2$). For most of our work it was simpler to take advantage of high-yield halogenolysis of the carbon–mercury bond and convert the arylmercury compounds to the easily characterizable aryl bromides or iodides.[6] Quite conveniently, the crude arylmercuries, still in the presence of excess

Scheme I



LiTMP and mercury salts, could be treated directly with bromine or iodine to effect these conversions. Control experiments showed that halogenation of the starting aromatic substrate after treatment with only LiTMP *or* $HgCl_2$ gave quite different results than with LiTMP/$HgCl_2$: with only LiTMP, the reaction mixture was very messy; the monobromide (ca. 10%) and 2-benzoyl-*N,N*-diethylbenzamide (ca. 40%) were identified, resulting presumably from halogenation and from condensation of the ortho-lithiated benzamide, respectively; with only $HgCl_2$, the starting material was recovered unchanged.

Table I summarizes our results for reactions of *N,N*-diethylbenzamide with LiTMP/$HgCl_2$ as a function of the major variables. Roughly, optimum conversion (entry 1) to the monosubstituted product was obtained by using short reaction times, temperatures near 0 °C, and close to stoichiometric quantities of the reacting species. Isolated yields near 80% were obtained in preparative runs. A LiTMP to $HgCl_2$ molar ratio of somewhat more than 2:1 was required. With less $HgCl_2$ (entry 2), no reaction of the aromatic compound was observed, probably because the active base was removed by the metathesis of eq 1. If a

$$2\text{LiTMP} + HgCl_2 \rightarrow 2\text{LiCl} + Hg(\text{TMP})_2 \qquad (1)$$

greater excess of base was used, the starting material was consumed more rapidly and more dimercuration was observed (vide infra), but the reactions were distinctly less clean (entries 3 and 4). Similarly, longer times (entry 5 vs 6) gave poorer mass balances, presumably because condensations were producing nonvolatile materials which escape GLC detection.

Excellent conversions were achieved with a $HgCl_2$ to substrate ratio of at least 1:1. With less $HgCl_2$ (entries 7

(1) Reviews on ortho-lithiation: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26* 1. (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (d) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957. Examples of amide activation for ortho-lithiation as a synthetic method: (e) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (f) Jacobs, S. A.; Harvey, R. G. *Tetrahedron Lett.* **1981**, *22*, 1093. (g) Beak, P.; Chen, C. *Tetrahedron Lett.* **1983**, *24*, 2945. (h) Shankaran, K.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 5022. (i) Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9. (j) Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145. For the use of LiTMP to lithiate ester-activated aromatic compounds, see: (k) Upton, C. J.; Beak P. *J. Org. Chem.*, **1975**, *40*, 1094.

(2) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724.

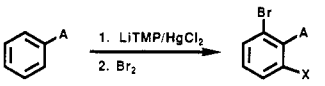
(3) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T.; Engel, P. *J. Org. Chem.* **1987**, *52*, 2100.

(4) Eaton, P. E.; Higuchi, H.; Millikan, R. *Tetrahedron Lett.* **1987**, *28*, 1055.

(5) For other applicable base/trap systems: Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. Nwokogu, G. C.; Hart, H. *Tetrahedron Lett.* **1983**, *24*, 5725. See also, ref 1j.

(6) General treatments of organomercury chemistry: LaRock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer-Verlag: Berlin, Heidelberg, 1985. Makarova, L. G.; Nesmeyanov, A. N. *The Organic Compounds of Mercury*; North-Holland Publishing Company: Amsterdam, 1967.

Table II. Metalation/Bromination of Ortho-Activated Benzenes



substrate, A =	molar ratio substrate/LiTMP/$HgCl_2$	reactn time, h	reactn temp, °C	products, X =	isolated yield, %
$CONEt_2$	1:6.3:3.0	1	20	Br	46
	1:4.5:2.0	2	0	Br	40
				H	19
	1:2.2:1.0	0.3	0	H	81
CO_2-*i*-Pr	1:4.5:2.0	2	0	H	77[a]
				Br	16
	1:4.3:2.0	0.5	0	H	83[a]
				Br	4
	1:6.3:3.0	1	20	H	62[a]
				Br	4
	1:2.5:1.0	3	0	H	77
CN	1:4.4:2.0	2	0	Br	5
	1:6.5:3.0	2	0	Br	16
Cl	1:4.1:2.0	2	0	Br	31

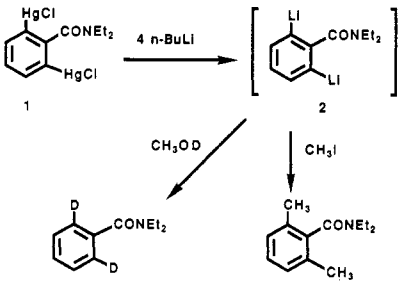
[a] The mono- and dibromides were not separated.

and 8), the reactions occurred, but more slowly and presumably by way of diarylmercury compounds. For such cases, the intermediate ArHgX must act as the transmetalating agent. Indeed, we know in the cubane series that phenylmercury chloride can be used successfully, albeit more expensively, in place of $HgCl_2$.

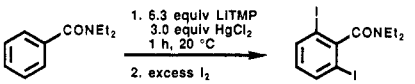
With longer reaction time (entry 9) or somewhat higher temperature (entry 10), particularly with substantial excesses of base and mercury salt, the metalation/transmetalation process gave dimercuration (and thence dihalogenated products). Now, it is known that direct ortho,ortho'-dilithiation of amide-activated aromatic compounds is not observed even if much stronger bases than LiTMP are used.[7,8] Therefore, the two mercury substituents here must be introduced by way of the iterant lithiation–mercuration–second lithiation–second mercuration sequence presented in Scheme I. The C–Hg bond apparently does not suppress a second metalation as does the much more polarized C–Li bond. Or, one might say, the amide group is not substantially coordinated to mercury and is "available" to facilitate the second ortho-lithiation.

As can be gleaned from Table II, and as was very obvious in practice, the amide group was by far the best activating substituent of those tried for the metalation reactions, combining rapid reactivity with resistance to side reactions, just as was already well-known from early ortho-lithiation competition experiments.[9] Nonetheless, other activating substituents, e.g. 4,4-dimethyl-2-oxazolino and isopropoxycarbonyl, were used with success. Such groups can be much more readily hydrolyzed than the tertiary amide group to the parent carboxylic acid, often a matter of real significance. The yields using chloro or cyano substituents as activators were not good, yet it may someday prove useful that the transmetalation method extends even to these extremes.

Scheme II



It is not our purpose to extol the obvious uses of the aromatic ortho-mercurated compounds available by this methodology.[6] We offer the one-pot synthesis of 2,6-diiodo-*N*,*N*-diethylbenzamide in 49% yield (nonoptimized) described in the Experimental Section as one clear indication of the power of the method (eq 2). Such *o*,*o*'-dihalo compounds, completely free of the para isomer, are not otherwise easy to come by.[1j]



(2)

Although it is not possible to ortho-lithiate directly an aromatic amide doubly under normal conditions, we have found that dilithiated aromatic amides can be made simply and fruitfully by the process we call "reverse transmetalation" and have defined in an earlier report.[10] Thus, as shown in Scheme II, reaction of the purified dimercury compound **1** with *n*-BuLi in THF at −60 °C resulted in a rapid transmetal equilibrium favoring, as expected from extension of simple acid–base theory, the dilithiated amide **2** and n-Bu_2Hg. Proof that **2** had indeed formed followed from isolation of the corresponding *o*,*o*'-dideuterio compound after the reaction mixture was quenched with CH_3OD. More interestingly, when the mixture was quenched at −60 °C with CH_3I, 2,6-dimethyl-*N*,*N*-diethylbenzamide was obtained in 61% yield.[11]

The methodology we have presented in this paper offers novel access to metalated aromatic compounds which

(7) For examples of dilithiated aromatic compounds: Winkler, H. J. S.; Wittig, G. *J. Org. Chem.* **1963**, *28*, 1733. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans 1* **1977**, 887. Hart, H.; Nwokogu, G. C. *Tetrahedron Lett.* **1983**, *24*, 5721. Crowther, G. P.; Sundberg, R. J.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657.

(8) Dilithiation was recently achieved on an aromatic tertiary amide, but only by way of halogen–lithium exchange; see ref 1j.

(9) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464. Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. Beak, P.; Tse, A.; Hawkins, J.; Chen, C.; Mills, S. *Tetrahedron* **1983**, *39*, 1983.

(10) Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948.

(11) The dimercury compound **1** does not react with water or CH_3I under such mild conditions.

should be of real use in synthesis, particularly for the preparation of ortho,ortho'-disubstituted benzenes, free of para isomers. However, it is necessary to point out that the utility of the method is reduced by difficulties in the present workup procedures. There are problems dealing with emulsions and hard-to-filter solutions and in removing mercury derivatives. These troubles might be lessened if zinc or magnesium rather than mercury salts were used.[4]

Experimental Section

^{1}H NMR spectra of $CDCl_3$ solutions containing Me_4Si as internal standard were taken in the FT mode at 500 MHz. Chemical shifts and coupling constants are reported to a precision of ±0.01 ppm and ±0.2 Hz, respectively. Infrared spectra were recorded on a Nicolet SX-20 FT-IR system with digital resolution of 1 cm^{-1}. Gas chromatography was performed on a Hewlett-Packard 5880 with a thermal conductivity detector using a 6 ft × 0.125 in stainless steel 3% OV-17 on 100–120-mesh Chromosorb W/HP column and a helium flow of 22 mL/min: T_i 180 °C; rate 5 °C/min; T_f 225 °C. For quantitative work, octadecane was used after appropriate calibration as an internal standard. Melting points are uncorrected. Elemental analyses were performed by Desert Analytical. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. 2,2,6,6-Tetramethylpiperidine (Aldrich) was distilled from KOH under nitrogen at reduced pressure (ca. 100 Torr) and then stored under argon over 4A molecular sieves. The detailed procedure[4] for the preparation of LiTMP used routinely in this laboratory was modified only slightly: the LiTMP solution was used after being aged 10 rather than 30 min at 0 °C.

2-Bromo-*N,N*-diethylbenzamide. LiTMP was prepared from *n*-butyllithium (34.5 mL, 1.44 M in hexanes, 49.7 mmol) and TMPH (0.68 g, 48 mmol) in 375 mL of THF. Mercuric chloride (5.80 g, 21.4 mmol) and *N,N*-diethylbenzamide (3.79 g, 21.4 mmol) were added. The murky, brownish gray mixture was stirred for 20 min at 0 °C. Bromine (4.4 mL) was added in 0.1–0.3 mL portions (ca. 15 °C exotherm) until the solution was bright orange. The mixture was stirred 90 min at 0 °C and then shaken with 150 mL of aqueous 10% Na_2SO_3 solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The extract was shaken with 200 mL of aqueous 5% $Na_2S{\cdot}9H_2O$. The opaque, precipitate-laden, aqueous emulsion was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was filtered through a pad of Celite, then washed with 100 mL each of aqueous 5% Cu_2SO_4 solution (1 M hydrochloric acid was used in later, smaller runs and was more effective in removing TMPH), water, and brine and then dried (Na_2SO_4). The solvents were removed, leaving 5.06 g of a dark brown oil. Distillation at 118–120 °C/0.5 Torr (lit.[12] mp 138–140 °C/2 Torr) gave 4.46 g of a yellow oil containing more than 95% (GLC) 2-bromo-*N,N*-diethylbenzamide, identified by GLC and spectral comparison to a sample synthesized independently from the corresponding acid chloride. The major contaminant was identified by GLC as 2,6-dibromo-*N,N*-diethylbenzamide.

2,6-Dibromo-*N,N*-diethylbenzamide. LiTMP was prepared from *n*-butyllithium (6.3 mL, 1.46 M in hexanes, 9.2 mmol) and TMPH (1.31 g, 9.27 mmol) in 25 mL of THF. Mercuric chloride (1.16 g, 4.27 mmol) and *N,N*-diethylbenzamide (252 mg, 1.42 mmol) were added with stirring. The ice bath was removed. The reaction mixture, initially gray-green, became brown within 5 min. The cloudy suspension gradually clarified. After 1 h the mixture was cooled to 0 °C. Bromine (0.9 mL) was added in 0.1-mL portions (ca. 15 °C exotherm) until the solution was bright orange. The mixture was stirred for 1 h at 0 °C, then diluted with 25 mL of diethyl ether, and washed with 25 mL of aqueous 10% Na_2SO_3 solution. The organic phase was shaken with 20 mL of aqueous 10% $Na_2S{\cdot}9H_2O$ solution. The insoluble black precipitate was removed by filtration on Celite. The aqueous phase was extracted with an additional 15 mL of ether, which was filtered through Celite. The combined organic phase was washed with 20 mL each of 1 M hydrochloric acid and water and then was concentrated in vacuo to 1 mL. CH_2Cl_2 (25 mL) was added; the solution was washed with 15 mL of brine and then dried (Na_2SO_4). Decantation and evaporation left 505 mg of a dark brown oil which solidified. Crystallization from diethyl ether gave 190 mg of dark crystals. The mother liquor was chromatographed on silica gel with 1:3 ethyl acetate/hexanes to give 108 mg of a yellow oil which solidified. The crystals and the solid were combined and crystallized from hexanes to give 218 mg (46%) of 2,6-dibromo-*N,N*-diethylbenzamide as white spars: mp 108–109.5 °C (lit.[13] mp 105.5–106.5 °C); ^{1}H NMR δ 7.50 (d, J = 8.1 Hz, 2 H), 7.05 (t, J = 8.1 Hz, 1 H), 3.60 (q, J = 7.2 Hz, 2 H), 3.16 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 7.2 Hz), 1.17 (t, J = 7.2 Hz, 3 H).

2,6-Diiodo-*N,N*-diethylbenzamide was prepared by substituting iodine for bromine in the previous experimental instruction. Crystallization from diethyl ether followed by recrystallization from hexanes gave 49% of the pure compound as fine white needles: mp 116.5–117.5 °C (lit.[1j] mp 112–114 °C); ^{1}H NMR δ 7.77 (t, J = 7.9 Hz, 2 H), 6.68 (t, J = 7.9 Hz, 1 H), 3.61 (q, J = 7.1 Hz, 2 H), 3.16 (q, J = 7.2 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 7.2 Hz, 3 H).

2,6-Bis(chloromercurio)-*N,N*-diethylbenzamide. Mercuric chloride (1.16 g, 4.27 mmol) and *N,N*-diethylbenzamide (252 mg, 1.42 mmol) were added to a solution of LiTMP at 0 °C prepared from *n*-butyllithium (6.0 mL, 1.52 M in hexanes, 9.1 mmol) and TMPH (1.30 g, 9.20 mmol) in 25 mL of dry THF. The ice bath was removed. The reaction mixture was stirred 1 h and then added to 10 mL of cold 2 M hydrochloric acid. The grey suspension was stirred 1 h, and then the volatile organics were removed in vacuo at room temperature. The suspension was diluted with 10 mL of water and stirred 30 min. After the suspension had settled, the slightly pink aqueous supernatant was carefully pipetted off. The lavender residue was stirred 30 min with 5 mL of CH_2Cl_2, then collected by filtration, air-dried, and extracted for 6 h with THF in a Soxhlet apparatus. The extract was boiled down to ca. 40 mL and cooled to room temperature. Ten milliliters of hexanes was added, precipitating a white solid which was collected and dried under vacuum to give 466 mg (50%) of 2,6-bis(chloromercurio)-*N,N*-diethylbenzamide as a fluffy, white solid: mp (sealed capillary, under argon) 273–275 °C; IR (KBr) ν 1588 (s), 1284 (m), 788 (m), 776 cm^{-1} (m); ^{1}H NMR δ 7.47 (t, J = 7.5 Hz, 1 H), 7.33 (d, J = 7.5 Hz, 2 H), 3.48 (q, J = 7.1 Hz, 4 H), 1.28 (t, J = 7.1 Hz, 6 H). Anal. Calcd for $C_{11}H_{13}Cl_2Hg_2NO$: C, 20.41; H, 2.02; N, 2.16. Found: C, 20.76; H, 2.12; N, 2.18.

2,6-Dimethyl-*N,N*-diethylbenzamide. 2,6-Bis(chloromercurio)-*N,N*-diethylbenzamide (173 mg, 0.27 mmol) was dissolved in THF (22 mL) under argon in a magnetically stirred flame-dried flask equipped with septum and a thermometer in direct contact with the reaction mixture. After almost all the solid had dissolved, the solution was cooled to –60 °C. *n*-Butyllithium (0.79 mL, 1.48 M in hexanes, 1.2 mmol) was added. The solution turned bright yellow. After 1 min, methyl iodide (300 mg, 3.1 mmol) was added; the color faded quickly. The reaction mixture was stirred 1 h at –60 °C and then allowed to warm to 0 °C. Iodine (0.34 g, 1.3 mmol) was added as a solid to destroy the byproduct n-Bu_2Hg. The solution was stirred for 1 h at 0 °C and then added to 15 mL of ether. The solvent was washed successively with 15 mL each of aqueous 15% Na_2SO_3 solution, aqueous 10% $Na_2S{\cdot}9H_2O$, and water and then concentrated in vacuo to about 2 mL. The residue was dissolved in 15 mL of CH_2Cl_2. The solution was washed with 10 mL of saturated brine and then dried (Na_2SO_4). Quantitative analysis by calibrated GLC showed the solution to contain 33.3 mg (61%) of 2,6-dimethyl-*N,N*-diethylbenzamide, identified by comparison to material synthesized independently from the corresponding acid chloride.[13] 2-Methyl-*N,N*-diethylbenzamide (3.9 mg, 8%), identified by similar synthesis, was also obtained. 2,6-Diiodo-*N,N*-diethylbenzamide (7%), probably resulting from iodination of undissolved starting material, was also found.

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Registry No. 1, 106711-49-3; $PhCO_2Pr$-i, 939-48-0; PhCN, 100-47-0; ClPh, 108-90-7; o-$BrC_6H_4CO_2Pr$-*i*, 59247-52-8; 2,6-$Br_2C_6H_3CO_2Pr$-*i*, 113586-25-7; 2,6-$Br_2C_6H_3CN$, 6575-12-8; 2-bromo-*N*,*N*-diethylbenzamide, 76041-86-6; *N*,*N*-diethylbenzamide, 1696-17-9; 2,6-dibromo-*N*,*N*-diethylbenzamide, 85370-72-5; 2,6-diiodo-*N*,*N*-diethylbenzamide, 97567-50-5; 2,6-dimethyl-*N*,*N*-diethylbenzamide, 57806-77-6; 2-methyl-*N*,*N*-diethylbenzamide, 2728-04-3; 2,6-dibromochlorobenzene, 19230-27-4.

Synthesis of a Model Hapten with Cyclohexanediol and α-Methylene-γ-butyrolactone Groups, a Synthetic Analogue of Poison Ivy and Tulipalin Allergens Connected with a Carbon Chain

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Potential skin sensitizers 1 and 1* with two different haptenic ends, (a) a cyclohexanediol group (saturated poison ivy analogue) and (b) an α-methylene-γ-butyrolactone moiety (tulipalin A), separated by a nine carbon atoms chain containing a double bond have been prepared. The trans,trans relationship in the substituted cyclohexanediol was secured by a tandem Michael addition–hydroboration reaction. Contrary to an earlier example of a double-headed hapten containing pyrocatechol and α-methylene-γ-butyrolactone ends, the cyclohexanediol–α-methylene-γ-butyrolactone does not show any tolerance induction to the α-methylene-γ-butyrolactone end. It therefore seems that induction of tolerance as well as sensitization requires the formation of covalent bond with a protein carrier.

Structure–activity relationship studies in allergic contact dermatitis (ACD) have shown that the induction of sensitization is controlled by the binding of the sensitizer (or hapten, i.e., an allergy-producing compound) with "immunocompetent structures" such as cells (in particular white cells or T-cells) or protein carriers.[1,2] Most of the skin haptens (i.e., incomplete allergen) are electrophilic[2] or "proelectrophilic"; i.e., they can be transformed in vivo into true electrophiles[2] and therefore show the capacity to form covalent bonds with epidermal proteins. However apparently nonelectrophilic skin sensitizers do exist[3,4] and are capable of forming strong hydrophobic bonds in particular with cell membranes. This is the case in particular of urushiols, a mixture of penta- and heptadecylcatechols containing 0, 1, 2, or 3 double bonds and present in the famous poison ivy (*Rhus radicans L.*) and poison oak (*Rhus diversiloba L.*). It is believed that these compounds insert into cell membranes through their hydrocarbon chains.[3]

Structural modifications to transform an allergen into a tolerogen (tolerance-producing substance) have attacted much interest.[5] By linking two well-known haptens, i.e., a catechol (poison ivy like) and a methylene lactone (present in particular in sesquiterpene lactones from Compositae) by a straight hydrocarbon chain, we recently observed a "tolerance" (immunological nonresponse to an allergen) directed toward the methylene lactone moiety.[6] In order words, animals treated with this "double-headed" hapten prior to sensitization could not be sensitized (i.e., made allergic) to a hapten only containing the methylene lactone moiety. Treatment with this "double-headed" hapten protected these animals against one end, the γ-lactone moiety. We interpreted this as resulting from the "burial" of the methylene lactone end inside the membrane, while the hydrophilic part of the molecule (catechol) was projected outwards. Thus only the emerging part of the molecule could be recognized by the T-cell receptors[7] leading to sensitization to the catechol part alone.

The question raised by this interpretation was as follows: was the observed tolerance to the lactone moiety a result of its "burial" into a cell membrane and/or was a preliminary recognition of the catechol moiety a necessary step? As the pyrocatechol is capable of transformation into an electrophile, an *o*-quinone, through oxidation, it is quite possible that nucleophilic proteins, for instance transmembrane proteins, could covalently bind to the hapten, transforming it into a complete antigen. The question therefore was as follows: what would happen if the catechol, a proelectrophilic moiety, is replaced by a hydrophilic group showing no or little electrophilic or proelectrophilic properties?

The aim of this work was to answer this question. We describe in this paper the syntheses and some biological results of the two new bihaptens 1 and 1* containing cyclohexanediol and methylene lactone ends. The cyclo-

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