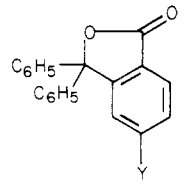
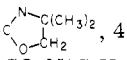
with benzophenone to give the lactones **12–15** in the yields indicated.



12, Y =  , 46%
13, Y = $-SO_2N(C_2H_5)_2$, 21%
14, Y = $-SO_2NHCH_3$, 60%
15, Y = -Cl, 60%

Reaction of *N,N*-diethyl-*N'*-methylterephthalamide (**16**) with 2 equiv of *s*-BuLi/TMEDA followed by deuteration or reaction with benzophenone gave predominantly *N,N*-diethyl-*N'*-methylterephthalamide-*3-d* (**17**) or the lactones **18** and **19**, respectively, as shown in Scheme II.[4,5] We presume the secondary amide would also take precedence over all other groups in Scheme I.[6] The superior directing ability of the amides may be rationalized in terms of associated species which are stabilized by intramolecular complexation.[1-3,7]

The high regiospecificities observed for the cases in Scheme I, in conjunction with preparative convenience, suggest amides should be the carboxylic acid derivative of choice for directing ortho lithiation. Moreover, since an amide function can be converted easily to an aldehyde, amine, alcohol, or alkyl group this approach appears advantageous for a wide variety of ortho substitutions. The secondary amide, which was reported first by Puterbaugh and Hauser to be a very good ortho-directing function,[2a] seems to be the most activating of the groups generally used, although the tertiary amide appears to be almost as effective.

It is particularly significant for the synthesis of polysubstituted aromatics that lithiation can be achieved adjacent to amides under conditions which do not affect other potentially useful functions.[2a,b,g,3a] The stability of the *o*-methoxy and *o*-chloro functions in **6** and **9** contrasts with the replacement of these or similar functions by organolithiums on reaction of the corresponding 2-aryloxazolines with alkyllithiums.[8] The directed metalation of **8** in the presence of the acidic benzylic hydrogens of the *p*-methyl group suggests useful subsequent conversions should be possible. It should be noted that we have found that the *o*-methyl group of *N,N*-diethyl-*o*-toluamide is metalated in preference to removal of the ortho proton, a result similar to that reported by Snieckus et al.[3a] Also, halogen–metal interchange occurs on attempted metalation of *N,N*-diethyl-*p*-bromobenzamide, a result which supplements the useful metalations of reactive bromo aromatics reported by Parham and co-workers.[9] Development of the metalative approach for synthesis, as well as studies of the underlying structure–stability relationships, are currently in progress.[10]

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work.

Registry No. **1**, 71888-21-6; **2**, 71888-22-7; **3**, 71888-23-8; **4**, 71888-24-9; **5**, 71888-25-0; **6**, 51674-10-3; **7**, 134-62-3; **8**, 2728-05-4; **9**, 10345-79-6; **10**, 15952-65-5; **11**, 7461-38-3; **12**, 71888-26-1; **13**, 71901-99-0; **14**, 71888-27-2; **15**, 71888-28-3; **16**, 71888-29-4; **17**, 71888-30-7; **18**, 71888-31-8; **19**, 71888-32-9; 2-(3-deuterio-4-(diethylaminocarbonylphenyl))-3,3-dimethyl-2-oxazolidine, 71888-33-0; *N,N*-diethyl-2-deuterio-4-[(diethylamino)sulfonyl]benzamide, 71888-34-1; *N,N*-diethyl-2-deuterio-4-[(methylamino)sulfonyl]benzamide, 71888-35-2; *N,N*-diethyl-2-deuterio-4-carboxybenzamide, 71888-36-3; *N,N*-diethyl-2-deuterio-4-[(dimethylamino)methyl]benzamide, 71888-37-4; *N,N*-diethyl-2-methoxy-6-deuteriobenzamide, 71902-00-6; *N,N*-diethyl-2-deuterio-3-methylbenzamide, 71888-38-5; *N,N*-diethyl-2-deuterio-5-methylbenzamide, 71888-39-6; *N,N*-diethyl-2-deuterio-4-methylbenzamide, 71888-40-9; *N,N*-diethyl-2-chloro-6-deuteriobenzamide, 71888-41-0; *N,N*-diethyl-2-deuterio-3-chlorobenzamide, 71888-42-1; *N,N*-diethyl-2-deuterio-4-chlorobenzamide, 71888-43-2.

(5) The formation of **18** and **19** is taken to show that the tertiary and secondary amides are competitive in directing ortho metalations but the relative yields of **18** and **19** do not necessarily reflect the relative amounts of dilithiated precursors.

(6) The present report may be considered to extend the work of Slocum and Jennings, which established that the secondary and tertiary sulfonamide, the secondary amide, and the (dimethylamino)methyl functions are more effective at directing ortho lithiations than are methoxy, β-(dimethylamino)ethyl, dimethylamino, trifluoromethyl, and fluoro substituents.[3c]

(7) For a quantitative study see P. Beak and B. Siegel, *J. Am. Chem. Soc.*, **96**, 6803 (1974).

(8) A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.*, **43**, 1372 (1978); A. I. Meyers and B. E. Williams, *Tetrahedron Lett.*, 223 (1978).

(9) W. E. Parham, D. C. Egberg, Y. A. Sayed, R. W. Thraikill, G. M. Keyser, M. Neu, W. C. Montgomery, and L. D. Jones, *J. Org. Chem.*, **41**, 2628 (1976), and references cited therein.

(10) In applications of these results it should be noted that diethylamide is preferred over the dimethylamide as the latter undergoes nucleophilic addition[2d] and methyl metalation.[3a]

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Ortho Metalations. Intermolecular Competition between Various Substituents

Summary: Equimolar amounts of phenyl oxazoline and substituted aromatics ($PhCONEt_2$, PhCONHMe, $PhSO_2NMe_2$, $PhSO_2NHMe$, $PhCH_2NMe_2$) were allowed to compete with 1 equiv of butyllithium to assess a reactivity series.

Sir: The methodology associated with ortho lithiation of aromatics has become an important synthetic tool in recent years.[1] Although a number of substituents are known to activate the ortho position toward deprotonation by strong bases, there has been only one systematic examination to assess the relative "activation" abilities. Slocum and Jennings[2] described a study which showed that, relative to the methoxyl group, there are a number of substituents more or less reactive to metalation. This was done by determining the site of metalation in a series of substituted anisoles. These authors concluded that SO_2NMe_2, SO_2NHMe, CONHMe, and CH_2NMe_2 were all more reactive toward metalation than the methoxy group, but did not assess the relative metalation abilities within this group.

Because of our interest in the metalation of aryl oxazoline (**2**)[3] and the apparent ease with which this occurs, we

(1) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, New York, 1974; H. W. Gschwend and H. R. Rodriguez, *Org. React.*, in press; P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).

(2) D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976).

(3) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975); H. W. Gschwend and A. Hamden, *ibid.*, **40**, 2008 (1975); A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978); A. I. Meyers and R. A. Gabel, *Tetrahedron Lett.*, 227 (1978); T. D. Harris, B. Neuschwander, and V. Boekelheide, *J. Org. Chem.*, **43**, 727 (1978); L. D. Veching and I. Vlattas, *ibid.*, **42**, 2649 (1977); J. A. Hauben, J. A. Miles, and J. A. Paton, *Org. Prep. Proced.*, **11**, 27 (1979); M. S. Newman and S. Kamar, *J. Org. Chem.*, **43**, 279 (1978).

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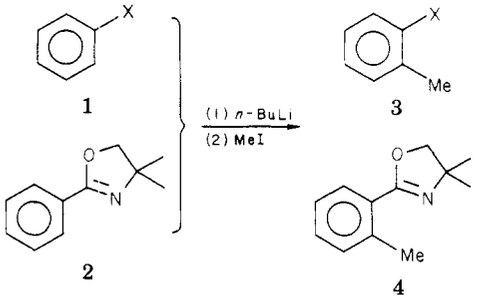
Table I. Competition between 1 and 2 for 1 Equiv of Butyllithium

	X	metalation temp, °C	% yield,[a] methylated products 3	4	% yield,[a] starting material 1	2
a	SO_2NMe_2	−45	88.5	<1	<1	77.5
b	SO_2NHMe	−45	41.0[b,c]	7.0	38.0[d]	60.0
c	$CON(i\text{-}Pr)_2$	−78	66.0	7.0	23.0	76.4
d	$CONEt_2$	−78[h]	70.0	15.0	<1[i]	67.0
e	CONHMe	−45	20.0[b,e,f]	77.8	80.0[f]	12.5
f	CH_2NMe_2	−45	<1	97.0	90[g]	<1

[a] Yields represent pure materials from preparative layer chromatography (silica gel, THF–hexane). [b] 2 equiv of *n*-butyllithium was used in order to remove amide proton prior to metalation. [c] Product was the *N,N*-dimethyltoluenesulfonamide. [d] Recovered as the *N,N*-dimethylbenzenesulfonamide. [e] HMPA added to dissolve the insoluble lithio amide prior to ring metalation. [f] Isolated as the *N,N*-dimethylbenzamide derivative. [g] Isolated as the benzyltrimethylammonium iodide. [h] *sec*-Butyllithium tetramethylethylenediamine used as base due to rapid displacement of the diethylamino group with *n*-BuLi (cf. L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, *J. Org. Chem.*, 41, 365 (1976). [i] Approximately 5% *o*-(benzoyl)-*N,N*-diethylbenzamide was recovered along qith 1d, which undoubtedly arose by the process mentioned in *h* above; cf. P. Beak, G. R. Brubacker, and R. F. Farney, *J. Am. Chem. Soc.*, 98, 3621 (1976).

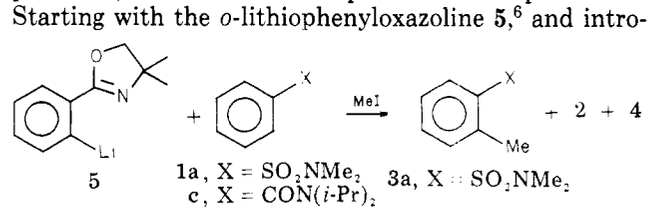
desired to explore the relative metalations of this species with those aryl derivatives considered to be more reactive than anisoles. We now report the results of an intermolecular competition[4] between monosubstituted benzenes **1** and phenyloxazoline (**2**) for 1 equiv of *n*-butyllithium.



a, X = SO_2NMe_2
b, X = SO_2NHMe
c, X = $CON(i\text{-}Pr)_2$
d, X = $CONEt_2$
e, X = CONHMe
f, X = CH_2NMe_2

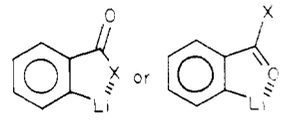
The lithio salts were trapped by addition of methyl iodide and the relative ratios of methylated compounds are given in Table I.[5] As seen from the competition experiments, the oxazoline **2** does not compete effectively with the sulfonamides or the benzamides **1a–d**. This is in good agreement with the results obtained by Beak.[4] However, the latter study chose the benzamide as the "anchor group" and measured activating abilities vs. a large number of other groups. In the present study, the oxazoline is chosen as the "anchor group" and it is found to be poorest with respect to the sulfonamide. Of particular interest was the ratio of methylated products derived from the competitive metalation of *N*-methylbenzamide (**1e**). Due to the insolubility of its *N*-lithio salt, direct competition for butyllithium in THF could not be assessed and, therefore, 2.0 equiv of HMPA was added to solubilize the salt. Addition of the phenyloxazoline and a second equivalent of *n*-butyllithium (−45 °C) gave, after isolation, the methylated oxazoline **4** as the major product (Table I). This is in direct contrast to the intramolecular results obtained by Beak and suggests that highly dipolar solvents could affect the relative metalation abilities.

In order to determine whether the isolated products result from direct metalation and not transmetalation processes, several crossover experiments were performed. Starting with the *o*-lithiophenyloxazoline **5**,[6] and introducing the benzenesulfonamide **1a** (−45 °C, 1.5 h) followed by methyl iodide gave, after PLC, 25.8% *o*-methyloxazoline (**4**), 40.3% phenyloxazoline (**2**), 40.3% methylated sulfonamide **3a**, and 39.0% sulfonamide **1a**. Based upon these results approximately 40% anion crossover occurred. When a similar experiment was performed using *N,N*-diisopropylbenzamide, no transmetalation occurred. This suggests that, on the basis of the present results, *N,N*-dimethylbenzenesulfonamide should ortho metalate more efficiently than all other groups thus far examined. In order to confirm this behavior, an intermolecular competition between *N,N*-dimethylbenzenesulfonamide and *N,N*-diisopropylbenzamide was carried out (1.0 equiv of *n*-BuLi, −45 °C) and, after quenching with methyl iodide, gave 85% *o*-methylbenzenesulfonamide (**3a**) and 15% of the *o*-methylbenzamide (**3c**).[7]

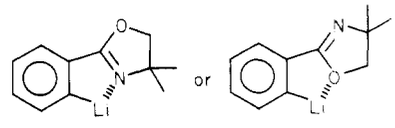


5 1a, X = SO_2NMe_2; c, X = $CON(i\text{-}Pr)_2$ 3a, X = SO_2NMe_2

This series of metalation abilities may be a result of the strain involved in chelating the *o*-lithium substituent. For the sulfonamides and benzamides a five-member ring chelate (A) may be more stable (less strain) than the oxazoline



A



B

chelate, which contains two fused five-membered rings. This strain may raise the energy of activation in reaching the transition state for metalation. These studies, coupled with the results of Beak,[4] indicate that considerable latitude is available when metalating aryl derivatives either intra- or intermolecularly.

Acknowledgment. We are grateful to the Army Research Office (Durham) for financial support of this work.

(4) An intramolecular competition study using these substituents has recently been performed in Professor Peter Beak's laboratory and the results are found in the accompanying paper. We are grateful to Professor Beak for allowing us to see his results prior to publication and agreeing to simultaneous reports.

(5) The ratios in Table I are in overall general agreement with ^1H NMR spectra of the crude reaction mixtures, which showed products and starting materials in similar ratios.

(6) An aliquot of **5** was quenched with methyl iodide giving 97% *o*-methyl derivative **4**, indicating the extent of the metalation prior to crossover.

(7) These results are synthetically useful as far as metalation efficiency is concerned, but no information regarding the transmetalation between these species has been gathered.

Registry No. **1a**, 14417-01-7; **1b**, 5183-78-8; **1c**, 20383-28-2; **1d**, 1696-17-9; **1e**, 613-93-4; **1f**, 103-83-3; **2**, 19312-06-2; **3a**, 67448-06-0; **3b**, 13440-22-7; **3c**, 6641-72-1; **3d**, 2728-04-3; **3e**, 2170-09-4; **3f**, 4525-48-8; **4**, 71885-44-4.

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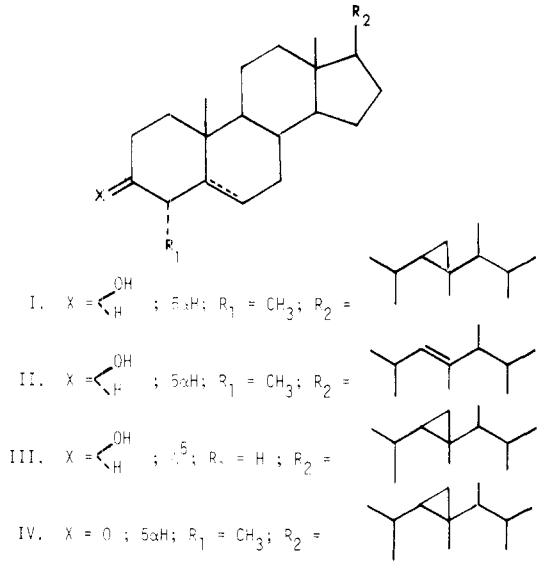
Dinoflagellate Sterols. 2. Isolation and Structure of 4-Methylgorgostanol from the Dinoflagellate *Glenodinium foliaceum*[1]

Summary: The dinoflagellate *Gonyaulax foliaceum* was found to contain four sterols, which were isolated and identified as cholesterol, 24-demethyldinosterol, dinosterol, and 4-methylgorostanol.

Sir: Dinoflagellates are unicellular organisms which along with diatoms and coccolithophores constitute what is commonly known as phytoplankton. Phytoplankton is the foundation for the food chain in the seas. Their distribution controls the whole pattern of life in the seas and is of great economic importance.

In our search of the origin of unusual sterols that have been isolated from marine invertebrates, especially from sponges, the dinoflagellate *G. foliaceum* was investigated for its sterol compositions.

The chloroform extract of the unialgal cultures of the *G. foliaceum*[2] gave a residue which after saponification afforded a sterol fraction consisting of four major sterols [cholesterol, 24-demethyldinosterol, dinosterol, and a new C_{31} sterol identified as 4-methylgorgostanol (1)] in the ratio



of 20:17:36:27 (GLC).[3] Sterol I was purified by high performance chromatography followed by preparative GLC,[4] and finally recrystallized by $CHCl_3$/MeOH to needles: mp 224–225 °C; $[\alpha]_D$ +6° (*c* 0.12, $CHCl_3$); $C_{31}H_{54}O$ (calcd *m/e* 442.417, found *m/e* 442.418).

The mass spectrum of the I[5] indicated the presence of a saturated steroid nucleus with a methyl group at C-4 (fragment ions *m/e* 289, 287, 271, 269, 247, and 229).[6,7,8] The intensities of the fragment ions [*m/e* 287 (100%), 271 (60%), 229 (27%)] were very close to that reported for dinosterol (II)[9] and 24-demethyldinosterol,[10] indicating the presence of dinosterol nucleus in the molecule. The presence of a methyl substituent at C-4 is also supported by the presence of the fragment ions at *m/e* 180, 179, and 125 corresponding $C_{12}H_{20}O$ and $C_{12}H_{19}O$ (ring A and B intact + CH_3) and $C_8H_{13}O$ (ring A + CH_3), respectively. The fragment ion at *m/e* 330 [77% ($C_{23}H_{30}O$ calcd 330.292, found 330.292)] corresponds to the cleavage of a cyclopropane ring in the side chain as in gorgosterol (III)[11] and 23-demethylgorgosterol.[12] The 100-MHz ^1H NMR spectrum of I has the characteristic absorption of a C-22,23 cyclopropane ring [δ −0.16 (1 H, d of d, J = 4 and 6 Hz), 0.06–0.3 (2 H, m), and 0.44 (1 H, d of d, J = 4 and 9 Hz)] as has been reported for gorgosterol[11] and acanthasterol.[13] The presence of eight alkyl-linked methyl signals [δ 0.63 (3 H, s), 0.70 (3 H, d, J = 6.5 Hz), 0.86 (3 H, s), 0.95 (3 H, s), 0.92 (3 H, d, J = 6.0 Hz), 1.05 (6 H, d, J = 6.3 Hz), 0.90 (3 H, d, J = 7 Hz)] was indicative of a molecule with additional methyl groups possibly at C-4, C-23, and C-24 (similar to those found in dinosterol). The presence of a methyl group at C-4 was confirmed by converting I into a ketone (mp 205–206 °C) by Jones oxidation. The CD curve of the oxidation product of I in dioxane (308, 298, and 289 nm) was similar to that reported for the ketone obtained from the oxidation of dinosterol.[9]

The ^1H NMR and mass spectral data of I implied the structure of 22,23-methylene-4α,23,24-trimethyl-5α-cholestan-3β-ol. The final proof of the structure of I was accomplished by the synthesis of 22,23-methylene-4α,23,24-trimethyl-5α-cholestan-3-one (IV), mp 205–206 °C, *m/e* 440 [(M^+, 4%), 328, 314, 287, 285, 269, 229], by methylation and Birch reduction of gorgost-4-en-3-one.[14] Compound IV and the oxidation poduct of I were found to be identical (GLC retention time, MS, and melting point).

The origin of unusual sterols isolated from marine invertebrates has been a subject of much discussion, since it is known that the sponges and possibly coelentrates are incapable of the de novo synthesis of sterols and carotenoids. It has been suggested that coelentrates and sponges may have acquired their sterols from dietary sources or from symbiotic microorganisms such as zooxanthellae.[15]

(1) Part 1: M. Alam, T. B. Sansing, E. L. Busby, D. R. Martiniz, and S. M. Ray, *Steroids*, **33**, 197 (1979).
(2) *Glenodinium foliaceum* (150 L) was cultured in 15-L solution bottles in enriched sea water medium as described in ref 1.
(3) The GLC analysis was performed on a 1.8 m, 1% OV-17 column: column temperature 250 °C, carrier gas 25 mL/min. Relative retention time of I to cholesterol was 2.7.
(4) Dinosterol and 4-methylgorgostanol were separated from each other only by preparative GLC. Preparative GLC was done on a 1.4 m, 5% OV-17 column (i.d. 1 cm) equipped with a glass splitter (80:20): column temperature 295 °C, carrier gas 60 mL/min.
(5) Mass spectrum (rel intensity) (20 ev) *m/e* 442 (30), 427 (6), 339 (10), 371 (11), 353 (20), 330 (77), 300 (55), 287 (100), 271 (61), 229 (27), 149 (46), 180 (5), 179 (11), 125 (16).
(6) R. Ryhage and S. Stenhagen, *J. Lipid Res.*, **1**, 361 (1960).
(7) J. Bergman, B. O. Lindgren, and C. M. Svahn, *Acta Chem. Scand.*, **19**, 1661 (1965).
(8) J. G. Tokes and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 5465 (1968).
(9) Y. Shimizu, M. Alam, and A. Kobayashi, *J. Am. Chem. Soc.*, **98**, 1059 (1976).
(10) M. Alam, K. H. Schram, and S. M. Ray, *Tetrahedron Lett.*, 3517 (1978).
(11) R. L. Hale, J. Leclercq, B. Tursch, C. Djerassi, R. A. Gross, Jr., A. J. Weinheimer, K. Gupta, and P. J. Scheuer, *J. Am. Chem. Soc.*, **92**, 2179 (1970).
(12) F. J. Schmitz and T. Pattabhiraman, *J. Am. Chem. Soc.*, **92**, 6073 (1970).
(13) Y. M. Sheikh, C. Djerassi, and B. M. Tursch, *Chem. Commun.*, 217 (1971).
(14) Prepared from gorgosterol: S. Popov, R. M. K. Carlson, A. Wegmann, and C. Djerassi, *Steroids*, **28**, 699 (1976).
(15) P. A. Steudler, F. J. Schmitz, and L. S. Ciereszko, *Comp. Biochem. Physiol.*, **56B**, 385 (1977).

0022-3263/79/1944-4466$01.00/0 © 1979 American Chemical Society