1.20 (H-2 and H-3), 2.07 br (H-14), and 1.44 (H-15) ppm.

X-ray Analysis of *Euserotin*. Crystals of 1 were prepared by slow crystallization from chloroform–hexane. They were orthorhombic, space group $P2_12_12_1$, with a = 7.270 (2) Å, b = 11.113 (4) Å, c = 27.226 (8) Å, and Z = 4. The intensity data were collected on a Hilger-Watts diffractometer (Ni-filtered Cu Ka radiation, θ–2θ scans, pulse height discrinimation). A crystal measuring approximately 0.25 × 0.4 × 0.7 mm was used for data collection. A total of 1733 reflections were measured for θ <57°, of which 1356 were considered to be observed [$I > 2.5\sigma(I)$]. The intensities of the five check reflections declined gradually to 90% of the original values at the end of the 2.5-day period required for data collection. The intensity data were corrected for this decline. At the end of the data collection periods, the two ends (along the a axis) of the crystal had become opaque, with only the center half of the crystal remaining clear.

The structure was solved by a multiple-solution procedure[32] and full-matrix least squares was used for all refinements. Twenty-four nonhydrogen atoms were found on the E map and two more were found on an electron density map on the basis of these atoms. A difference map calculated after isotropic refinement of these 26 atoms (all but C(21)) showed the presence of disordered solvent in the crystal. Three peaks, two of which were located on crystallographic twofold axes, were assigned carbon scattering factors. The refinement was continued with anisotropic thermal parameters for the 46 carbon and oxygen atoms of the molecule of euserotin and isotropic temperature factors for the three "solvent" atoms. C(21) was found on a difference map calculated after this refinement. The positions of all hydrogen atoms were calculated on the basis of the molecular geometry. For the final refinement anisotropic thermal parameters were used for all carbons and oxygens of euserotin except C(21) and isotropic temperature factors were used for C(21), the three "solvent" atoms, and the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.089 and R_w = 0.102 for the 1356 observed reflections. The final difference map has no peaks greater than ±0.3 e Å^{-3}.

(32) G. Germain, P. Main, and M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

Registry No. **1a**, 70550-00-4; **1b**, 70550-01-5; **1e**, 6750-25-0; **2a**, 70527-88-7; **2b**, 57718-81-7; **2d**, 56245-55-7; **3**, 70527-89-8; pectolinarigenin, 520-12-7; hispidulin, 1447-88-7.

Supplementary Material Available: Tables III–VII listing final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles of euserotin (5 pages). Ordering information is given on any current masthead page.

Notes

Ring-Opening Reactions of Aziridines with Organometallics

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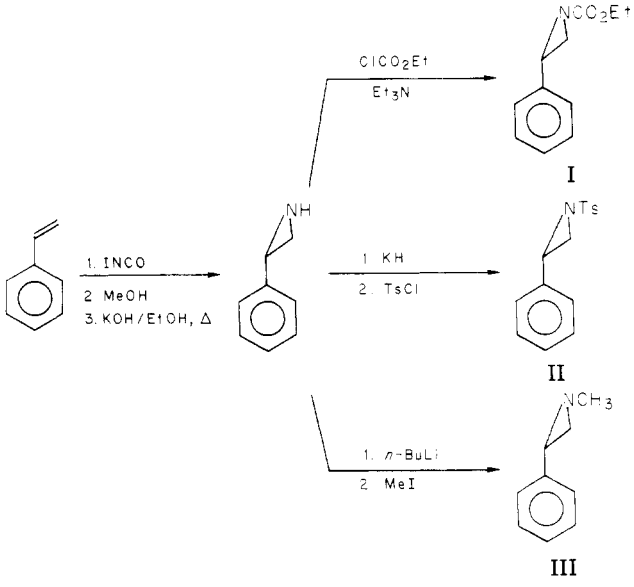
In our efforts to further the use of small-ring heterocycles in the synthesis of alkaloid systems, we initiated studies to ascertain the ability of various organometallics to effect cleavage reactions of N-substituted aziridines.[1] While the study was primarily aimed at defining the nature of the metal required to effect this transformation under the mildest of conditions, we were also concerned with the regiochemical outcome of this reaction when a choice between attack at a secondary carbon bearing a phenyl group or attack at a primary carbon was possible.

It should be noted that, while the reactions of epoxides with organometallics have been relatively well studied,[2] very few literature guidelines exist for conducting similar reactions on the nitrogen counterparts of these small-ring heterocycles. The only prominent reactions in this context are (a) the ring opening of aziridines in polar solvents by stabilized carbanions such as those derived from malonic esters to afford substituted α-pyrrolidones, (b) a report of attack at the ring carbon of N-carbethoxyaziridine by trityllithium, and (c) the observation that lithium dibutylcuprate gives ring-carbon attack for a rather special N-acylaziridine whereas the corresponding magnesium and lithium reagents react at the carbonyl group.[3]

The N-substituted derivatives of 2-phenylaziridine were chosen as the substrates for our studies, since these compounds would clarify the extent to which bond rupture in the transition state is guided by resonance stabilization.

Scheme I



† Fellow of the Alfred P. Sloan Foundation.

(1) For an excellent review on aziridines, see O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines", Academic Press, New York, 1969.

(2) R. L. Letsinger, J. G. Traynham, and E. Bobko, *J. Am. Chem. Soc.*, **74**, 399 (1952); R. J. Anderson, *ibid.*, **92**, 4978 (1970); R. W. Herr, D. M. Wieland, and C. R. Johnson, *ibid.*, **92**, 3813 (1970); R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970); J. Staroscik and B. Rickborn, *ibid.*, **93**, 3046 (1971); D. M. Wieland and C. R. Johnson, *ibid.*, 3047 (1971); J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *ibid.*, **94**, 4342 (1972); R.-D. Acker, *Tetrahedron Lett.*, 2399 (1978).

(3) (a) H. Stamm, *Chem. Ber.*, **99**, 2556 (1966); (b) A. Hassner and A. Kascheres, *Tetrahedron Lett.*, 4623 (1970); (c) Y. Kishi et al., *J. Org. Chem.*, **40**, 2009 (1975).

0022-3263/79/1944-2788$01.00/0

Table I. Reactions of Aziridines with Organometallics

entry	aziridine	organometallic	reacn conditions temp/time/solvent	product(s)	isolated yield, %
1	I	CH_3Li	0 °C/2 h, then room temp/2 h/THF		85
2	I	$H_2C{=}C{=}C(OMe)Li$	−20 °C/7 h/THF	recovd starting material	
3	I	CH_3MgBr	0 °C/3 h, then room temp/3 h/Et_2O	$PhCH(CH_3)CH_2NHCO_2Et$	48
4	I	$CH_2{=}CHCH_2MgBr$	room temp/6 h/Et_2O-THF (1:1)	$PhCHBrCH_2NHCO_2Et$	75
5	I	$(CH_3)_2CuLi$	0 °C/6 h/Et_2O	$PhCH(CH_3)CH_2NHCO_2Et$	98
6	I	$(n\text{-}Bu)_2CuLi$	0 °C/4 h/Et_2O	$PhCH(n\text{-}Bu)CH_2NHCO_2Et$ + $PhCH(NHCO_2Et)CH_2\text{-}n\text{-}Bu$ (3:1)	70
7	I	$(CH_2{=}CH)_2CuLi$	−70 °C/3 h, then 0 °C/3 h/Et_2O	decompn	
8	I	$CH_3Cu{\cdot}BF_3$	−70 → 0 °C gradually, then room temp/1 h/Et_2O	$PhCH(CH_3)CH_2NHCO_2Et$	95
9	II	CH_3Li	room temp/10 h/THF	decompn	
10	II	CH_3MgBr (1 equiv)	0 °C/3 h, then room temp/3 h/Et_2O-THF (1:2)	$PhCH(NHTs)CH_2CH_3$ + $PhCH(CH_3)CH_2NHTs$ (1:3.5)	41
11	II	CH_3MgBr (4 equiv)	room temp/10 h/Et_2O-THF (1:2)	$PhCH(CH_3)CH_2NHTs$	46
12	II	$CH_2{=}CHCH_2MgBr$ (4 equiv)	room temp/24 h/THF	$PhCH(CH_2CH{=}CH_2)CH_2NHTs$	94
13	II	$CH_2{=}C(CH_3)CH(O(THP))Li + MgBr_2$ (4 equiv)	−70 °C/3 h/Et_2O-THF (2:3.5)	$PhCHCH_2NHTs$ | $(THP)O{-}CH{-}C(CH_3){=}CH_2$	56
14	II	$(CH_3)_2CuLi$	−78 °C/1 h/Et_2O	$PhCH(CH_3)CH_2NHTs$ + $PhCH(NHTs)CH_2CH_3$ (1:2)	70
15	III	$(CH_3)_2CuLi$	−70 °C/3 h, then 0 °C/3 h/Et_2O	decompn	
16	III	$CH_3Cu{\cdot}BF_3$	−70 °C/5 h/Et_2O	decompn	

The three aziridines I–III were prepared from the readily available 2-phenylaziridine, a product obtained in high yield by application of the Hassner and Heathcock iodoisocyanate route to styrene.[4] This N-unsubstituted aziridine was subsequently treated with $Et_3N/ClCO_2Et$,[5] KH/TsCl, or n-BuLi/CH_3I[6] to afford aziridines I–III, respectively (Scheme I).

Our survey of the behavior of these aziridines toward organometallics was confined to an investigation of the lithium, magnesium, and copper reagents. Preliminary studies revealed that the lithium reagents were generally unsatisfactory, for decomposition of the aziridine or displacement of the N-substituent (Table I, entries 1 and 9) ensued. Ring cleavage was achieved, however, in good yield with the latter two reagents.

The *N*-tosylaziridine II was expectedly found to be a more reactive substrate than aziridine I, while aziridine III proved quite unsuitable for these studies due to its general instability (no isolable products were observed for entries 15 and 16).

The reaction of I and II with homocuprates (1.2 equiv) was observed to proceed in good overall yield (entries 5, 6, and 14). Only the less reactive lithium divinylcuprate failed to afford an isolable product.[7]

Of considerable interest is the finding that reaction of I with the newly introduced methylcopper–boron trifluoride complex ($MeCu{\cdot}BF_3$ or $Me^-BF_3Cu^+$)[8] was found to proceed under milder conditions than observed for the corresponding homocuprate. The higher Lewis acidity of this reagent presumably assists in bond rupture through interaction of the complex with the unshared electron pair of nitrogen. This observation demands further exploration, for these reagents may be attractive for effecting ring-cleavage reactions of epoxides as well.

The magnesium reagents (1 equiv used unless indicated otherwise) also reacted with I and II to afford phenethylamines, although in yields somewhat lower than obtained for the cuprates. This observation was particularly important, for as in entry 13, the generation of the Grignard reagent from the corresponding lithium derivative of this allyloxy carbanion is readily brought about on addition of anhydrous magnesium bromide. In contrast, only low yields of product were obtained when attempts were made to prepare the corresponding copper reagent and utilize this for ring cleavage. It is also important to note here that the addition of this ambident nucleophile to aziridine II has occurred with high site selectivity α to oxygen.[9] The reactions of such functionalized allyloxy anions with three-membered heterocycles has not to our knowledge been previously recorded.

In all cases examined, the regiochemistry of these ring openings is consistent with a mechanism lying somewhere between the purely A-2 and A-1 extremes. Transfer of the alkyl substituent occurs to that carbon atom best able to accommodate some carbonium ion character. A pure A-2 transition state would, of course, require attack at the less hindered carbon.[10] These observations are all well in line with results recorded for the ring opening of epoxides by numerous workers several decades ago.[11] In addition, it has previously been noted that the proportion of reagents used in these ring-cleavage reactions has an important effect on the regiochemistry of this process.[12] This product dependency factor was most strikingly noted in the present instance when II was treated with 4 equiv of methylmagnesium bromide rather than the 1–1.2 equiv of reagent

(4) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).
(5) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964).
(6) H. Gilman, *J. Am. Chem. Soc.*, **67**, 2106 (1945).
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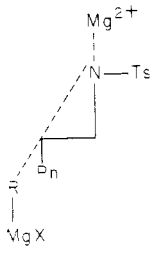
(8) K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977); *J. Organomet. Chem.*, **156**, C9 (1978).

(9) The ability to control α–γ regioselectivity in the reactions of allyloxy carbanions by manipulation of the metal counterion has previously been noted. See D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974), and references cited therein.
(10) G. Berti, G. Camici, B. Macchia, F. Macchia, and L. Monti, *Tetrahedron Lett.*, 2591 (1972); J. Biggs, N. B. Chapman, A. F. Finch, and V. Wray, *J. Chem. Soc. B*, 55 (1971).
(11) R. Fuchs and C. A. Vander Werf, *J. Am. Chem. Soc.*, **76**, 1626, 1631 (1954).
(12) E. L. Eliel in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, pp 106–1[illegible].

generally used in the previous cases (cf. entries 10 and 11). The presence of the excess reagent caused ring opening to become completely regiospecific without affecting the isolated yield. The ubiquitous push–pull mechanism again nicely accommodates this result wherein the excess Grignard reagent, functioning as a Lewis acid, now provides a tug on nitrogen and increases the extent of bond rupture in the transition state. The increased ionizing power of the solvent does, of course, also play an important role here.[13]



These studies, while indicating several new areas for exploration, should provide some needed guidelines for the reactions of organometallics with N-activated aziridines. The use of these compounds in natural product synthesis is currently being explored.

Experimental Section

General Procedures. The ^1H NMR spectra were taken on a Varian T-60 instrument, using tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 700 spectrometer. The cuprous iodide was prepared from cupric sulfate, potassium iodide, and sodium thiosulfate. The ether was dried by distillation from sodium–benzophenone ketyl. The organolithium and -magnesium reagents were obtained from commercial sources.

Reaction of Aziridine I with Lithium Dimethylcuprate (Entry 5). To 114 mg (0.6 mmol) of freshly dried cuprous iodide in 7 mL of ether cooled to 0 °C was added 0.84 mL of methyllithium (1.4 M, 1.2 mmol). After the solution was stirred for 10 min at 0 °C and 30 min at room temperature, the cuprate was cooled to −70 °C and 96 mg (0.5 mmol) of *N*-carbethoxy-2-phenylaziridine was added. The reaction mixture was gradually warmed to 0 °C and maintained at this temperature for 6 h. The mixture was then quenched by addition of 8 mL of a saturated ammonium chloride solution and the product extracted with ether. The crude isolated material was purified by silica gel chromatography with methylene chloride as eluent to yield 101 mg (98%) of the ring-opened product: IR ($CHCl_3$) 3600–3500, 1720 cm^{-1}; NMR (CCl_4) δ 7.23 (s, 5 H), 4.83 (broad s, 1 H), 4.33 (q, 2 H, J = 7 Hz), 3.25 (m, 2 H), 2.83 (m, 1 H), 1.34 (d, 3 H, J = 7 Hz), 1.17 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) m/e 207 (M^+).

Reaction of Aziridine I with Methyl Copper–Boron Trifluoride (Entry 8). To 190 mg (1 mmol) of freshly dried cuprous iodide in 3 mL of ether cooled to 0 °C was added dropwise 0.75 mL of methyllithium (1.4 M, 1 mmol). After 30 min at 0 °C, the methylcopper was cooled to −70 °C and 0.13 mL (1 mmol) of boron trifluoride etherate was added. The resulting mixture was stirred for 10 min, and then 94 mg (0.5 mmol) of *N*-carbethoxy-2-phenylaziridine was added. The reaction mixture was gradually warmed to room temperature and kept at this temperature for an additional 1 h. Workup as in the above experiment gave 96 mg (95%) of the ring-opened carbamate.

Reaction of Aziridine II with Allylmagnesium Bromide (Entry 12). To a solution of 68 mg (0.25 mmol) of *N*-tosyl-2-phenylaziridine in 2 mL of ether initially cooled to 0 °C was added 0.8 mL of a 1.3 M solution of allylmagnesium bromide in ether. The reaction mixture was stirred at room temperature for 24 h, quenched by addition of 8 mL of a saturated ammonium chloride solution, and extracted with ether. The crude isolated product was purified by silica gel chromatography with 10% ethyl acetate–hexane as eluent to afford 74 mg (94%) of the ring-opened product: IR ($CHCl_3$) 3700, 3600, 1340, 1170 cm^{-1}; NMR (CCl_4) δ 7.63 (d, 2 H, J = 7 Hz), 6.90–7.40 (m, 7 H), 5.84–4.70 (m, 3 H), 4.40 (broad t, 1 H), 2.14–3.65 (m, 5 H), 2.36 (s, 3 H); mass spectrum (70 eV) m/e 306, 250, 177 (base).

Reaction of Aziridine II with an Allyloxy Carbanion (Entry 13). To a solution of the allylic organometallic derived from *sec*-butyllithium treatment of the tetrahydropyranyl ether of methallyl alcohol (2 mmol in 3 mL of THF)[9] cooled to −70 °C was added a freshly prepared solution of magnesium bromide (312 mg, 1.70 mmol) in 2 mL of ether. After 10 min of stirring, 68 mg (0.25 mmol) of *N*-tosyl-2-phenylaziridine in 0.5 mL of THF was added, and the reaction mixture was maintained at −70 °C for 3 h. The mixture was quenched with 8 mL of a saturated ammonium chloride solution and extracted with ether. The crude isolated product was purified by silica gel chromatography with 25% ethyl acetate–hexane as eluent to yield 60 mg (56%) of the ring-opened product: IR ($CHCl_3$) 3700, 3600, 1340, 1170 cm^{-1}; NMR (CCl_4) δ 7.60–7.96 (overlapping d, 2 H), 7.00–7.49 (m, 7 H), 5.00 (broad s, 1 H), 4.75–4.96 (m, 2 H), 4.27–4.60 (m, 1 H), 3.85–4.25 (m, 1 H), 2.65–3.70 (m, 5 H), 2.27 (s, 3 H), 1.17–1.90 (m, 9 H); mass spectrum (70 eV) m/e 155, 84 (base).

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Registry No. I, 70197-04-5; II, 24395-14-0; III, 4164-25-4; CH_3Li, 917-54-4; $H_2C{=}C{=}C(OMe)Li$, 61186-66-1; CH_3MgBr, 75-16-1; $CH_2{=}CHCH_2MgBr$, 1730-25-2; $(CH_3)_2CuLi$, 15681-48-8; $(n\text{-}Bu)_2CuLi$, 24406-16-4; $(CH_2{=}CH)_2CuLi$, 22903-99-7; $CH_3Cu{\cdot}BF_3$, 70197-05-6; $CH_2{=}C(CH_3)CH(O\text{-}THP)Li$, 70197-06-7; 2-phenylaziridine, 1499-00-9; ethyl 2-phenylpropylcarbamate, 70197-07-8; ethyl 2-bromo-2-phenylethylcarbamate, 63409-27-8; ethyl 2-phenylhexylcarbamate, 55150-58-8; ethyl 1-phenylhexylcarbamate, 70197-08-9; *N*-tosyl-1-phenylpropylamine, 70197-09-0; *N*-tosyl-2-phenylpropylamine, 70197-10-3; *N*-tosyl(2-phenyl-4-pentenyl)amine, 70197-11-4; *N*-tosyl(4-methyl-2-phenyl-3-tetrahydropyronyloxy-4-pentenyl)amine, 70197-12-5.

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Synthesis of a Key Chiral Intermediate for 12-Hydroxyprostaglandins

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Grieco and co-workers recently described the synthesis of (±)-12-hydroxyprostaglandin $F_{2\alpha}$ methyl ester and reported that, when compared to $PGF_{2\alpha}$, the substance has a comparable activity in terminating pregnancy in the hamster but has minimal smooth muscle stimulating activity on gerbil colon and hamster uterine strips.[1] The 12-OH-$PGF_{2\alpha}$ would appear, therefore, to possess luteolytic activity with a diminished potential for side effects such as diarrhea. We wish to report here a remarkably simple synthesis of one of their key intermediates (**5b**) in optically active form having the absolute configuration corresponding to that of natural prostaglandins.

Optically active intermediates of type 1 are available by many synthetic routes,[2-5] and such compounds are readily

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