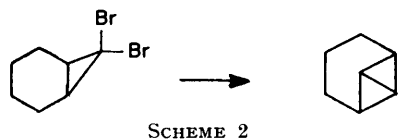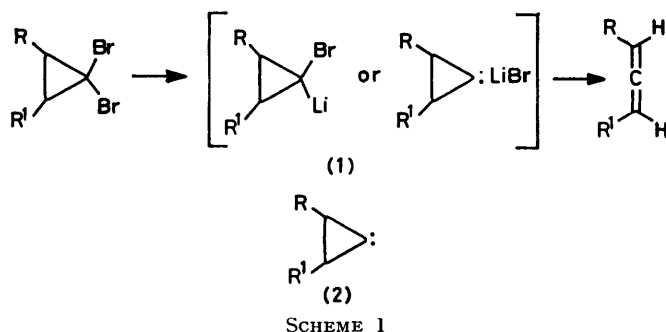# The Reaction of 1,1-Dibromocyclopropanecarboxamides with Methyl-lithium

By **Mark S. Baird** * and **Anthony G. W. Baxter**, Department of Organic Chemistry, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU

On reaction with one equivalent of methyl-lithium at below −60 °C followed by aqueous quenching, the dibromo-amides (5) and (6) were reduced to monobromides (10) and (9). An intermediate could be partially trapped as a mono-deuteride (15) by quenching with D_2O at low temperature, or as (14) by addition of benzaldehyde, but could not be trapped by addition of Me_3SiCl or CO_2; however, quenching with D_2O after the reaction solution had been warmed to 35 °C led to (10) with no deuterium incorporation. The source of the proton in this last reaction was the solvent, ether. Treatment of (5) with 2 mol equiv. MeLi at −60 °C also led after low-temperature aqueous quenching to (10); if the temperature was rapidly raised to 35 °C two products, (20) (major) and (19) (minor), were isolated after quenching. If, however, (5) was treated with 1 mol equiv. MeLi at −60 °C, followed by very slow addition of a second mol equiv. at 35°, (19) was the major product. The monobromide (10) is an intermedi-ate in both these reactions, and indeed leads to (19) and (20) in similar proportions to those from (5) when treated with 1 equiv. MeLi either rapidly or dropwise at 25—35 °C; reaction of (9) with 1 equiv. MeLi leads, however, to the ketone (11 ; X = Me).

THE reaction of 1,1-dibromocyclopropanes with an alkyl-lithium is a well documented synthesis of allenes (Scheme 1).[1] The reaction proceeds through carbenoids such as (1) related to the free cyclopropylidene (2). Lithiobromides (1) have indeed been trapped by reaction with electrophiles; thus 7,7-dibromobicyclo[4.1.0]hep-tane can be converted to the 7-lithio-7-bromo-com-

may promote insertion. Thus, compounds (4; $n = 1$, X = NR, O, or S) react with methyl-lithium *via* insertion of the corresponding cyclopropylidene into a 5,6-related

SCHEME 3

C–H bond, in competition with ring-opening to the allenes.[5-7] It should be noted however that no such insertion occurs for compounds (4; $n = 2$) and (4; $n = 3$). Few reactions of 1,1-dibromocyclopropanes con-taining other functional groups such as esters, ketones, or acids, which might intercept either the alkyl-lithium or the intermediate carbenoid, have been described, and in these cases the usual products are those formed by reduc-tion, such as cyclopropanes and monobromocyclo-propanes.[8-11]

We now report the reactions of amides (5) and (6) with methyl-lithium, when by varying the conditions we observe both reduced and carbenic products.

(1)

(2)

SCHEME 1

SCHEME 2

pound [2] at below −100 °C, and the latter can be quenched with a proton source to produce the corresponding mono-bromide or warmed to above −100 °C to lead to products of carbenic decomposition.†

In certain circumstances cyclopropylidenes (2) or related carbenoids (1) can undergo reactions other than rearrangement to allenes. Thus intramolecular inser-tions into carbon–hydrogen bonds or additions to carbon–carbon double bonds have been observed leading, for example, to bicyclo[1.1.0]butanes (Scheme 2)[3] or to the extremely reactive hydrocarbon (3) (Scheme 3).[4] The presence of functional groups such as ethers or amines
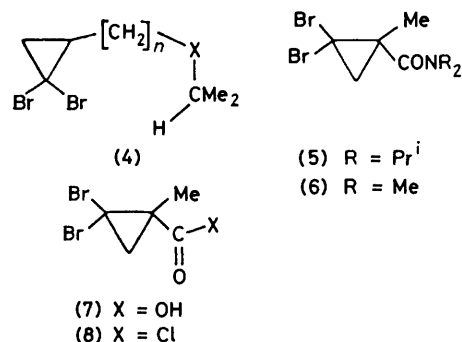
(4)

(5) R = Pr^i
(6) R = Me

(7) X = OH
(8) X = Cl

† These we regard as products which are typical of those ex-pected from a carbene, though they may in fact be derived from a carbenoid.

RESULTS AND DISCUSSION

The acid (7) has been obtained by Stein [9] by reaction of methyl methacrylate with dibromocarbene (generated

from PhHgCBr$_3$ or CHBr$_3$–KOBu^t), followed by hydrolysis. We have obtained (7) in one step by reaction of the ester with dibromocarbene (generated by phase-transfer catalysis), followed by *in situ* hydrolysis. A similar method has recently been reported by Skattebøl [12] and by Sydnes.[13] Conversion of the acid (7) into the acid chloride (8) (86%) followed by treatment with the appropriate amine afforded (5) (80%) and (6) (67%).

The n.m.r. spectra of both (5) and (6) indicated restricted rotation about the amide linkage. The dimethylamide showed two methyl signals at δ 2.92 and 3.14; no coalescence of these signals occurred at 335 K.

The di-isopropylamide showed complex signals in the methyl region, but two distinct septets were obtained for the isopropyl methine hydrogens at δ 3.36 and 4.06; again, raising the temperature to 335 K caused no coalescence, and ΔG for coalescence was calculated to be >81 kJ mol^{-1}.[14]

(i) *Reaction of* (5) *and* (6) *with* MeLi (1.1 *mol equiv.*).— Reaction of (5) and (6) with MeLi (1.1 mol equiv.) in ether at below −60 °C, followed by quenching with water at that temperature, led to the monobromides (10) and (9), respectively, in good yield. Both amides were resistant to acid and base hydrolysis and so were


(5) R = Pr^i
(6) R = Me

(10) R = Pr^i
(9) R = Me
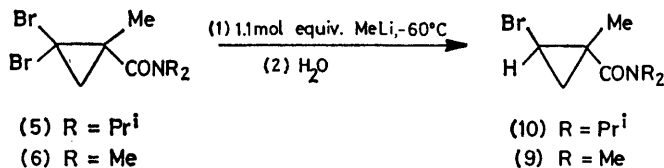
not directly degraded to the known acid (11; X = OH).[9] However, reaction of (9) with a second mol equiv. of MeLi at 25—35 °C led to (11; X = Me) (95%), which was converted to (11; X = OH) by the iodoform reaction and shown to be identical with authentic material; reaction of (6) with MeLi (2.2 mol equiv.) at −60 °C followed by refluxing also led to (11; X = Me). The n.m.r. spectra of (10) and (9) provided further evidence of the configuration at C-2, chemical shifts and coupling constants being close to those of (11; X = OMe).[12] The isopropyl-CH protons of (10) appeared as two very broad signals which coalesced to a broad multiplet at 315 K; ΔG was calculated as 75.4 ± 0.7 kJ mol^{-1}, and was smaller than that of (5), in agreement with the assigned configuration.* The monobromide (9) showed two distinct Me-signals in the n.m.r. spectrum, which on warming coalesced to a single line at 294 K, corresponding to a ΔG of 73.9 ± 0.7 kJ mol^{-1}.

The formation of (9) and (10) from (6) and (5) implies that the presumed intermediates (12; R = Me or Pr^i)

* The interpretation of rotational barriers in amides R′CONR$_2$ in terms of the size of R′ is complicated. Thus when the groups are relatively small an increase in the size of R′ can *decrease* the barrier (*e.g.* T. H. Siddall, W. E. Stewart, and F. D. Knight, *J. Phys. Chem.*, 1970, **74**, 3580) whereas when bulky groups are present the reverse result is obtained (A. Mannschreck, A. Mattheus, and G. Rissmann, *J. Mol. Spectroscopy*, 1967, **23**, 15). In the cases reported herein R′ is a particularly bulky group and the latter situation may be expected; this is borne out in practice.

must be stabilised by interaction between the lithium and the oxygen or nitrogen of the side chain, thus suppressing carbenic reactions. Such 1,5-interactive stabilisation has been proposed by Taylor [15] to explain

(11)

(12)

(13)

(14)

(15)

(16)
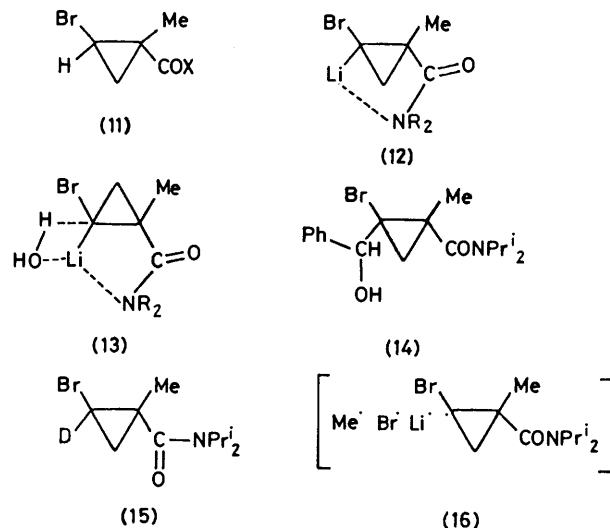
the stereoselective formation of 7-halogeno-7-lithio-3-oxabicyclo[4.1.0]heptane from the 7,7-dihalogeno-compound. Protonation of (12) would occur stereospecifically with retention of configuration, possibly by interaction with the water molecule in a four-centred intermediate (13).[16]

Lithiobromides related to (12) have been trapped by a range of electrophiles.[2,15] Reaction of (5) with MeLi (1.1 mol equiv.) at below −60 °C followed by addition of Me$_3$SiCl, refluxing, and then quenching with water gave only (10); addition of CO$_2$ in place of Me$_3$SiCl led to no appreciable acidic products. However, (12; R = Pr^i) could be trapped by addition of benzaldehyde to the low-temperature reaction, when (14) † was obtained. Attempts to alkylate (12; R = Pr^i) with methyl or allyl bromide were not successful. When (5) was treated with MeLi (1 mol equiv.) at −60 °C and the products were quenched immediately with D$_2$O at below −40 °C, a mixture of (15) (63—70%) and (10) (37—30%) was obtained. When the solution was set aside for 30 min at −60 °C before quenching, there was no difference in the deuterium incorporation within experimental limits. The low incorporation, was not, therefore, due to slow absorption of water from the atmosphere. Indeed (5) could be treated with 2 mol equiv. MeLi at −60 °C and quenched at that temperature to give (10) as the only major product, and quenching with D$_2$O again gave a maximum of 70% incorporation. Anomalous partial deuteriations [15,17] and reductions [18] have been noted in related reactions but no convincing explanation has been offered; one possible proton source would be the alkyl

† A second (presumed) diastereoisomer of (14) was also obtained but this could not be effectively separated from a third product, (10). Compound (14) was unusual in that restricted rotation led to four doublets in the n.m.r. spectrum for the isopropyl methyl groups, as well as two isopropyl–CH signals.

halide formed in the initial reaction of the dibromide with RLi.[18]

Ward *et al.* have postulated a radical mechanism for the reaction of a dihalogenocyclopropane with ethyl-lithium, and have observed CIDNP effects. One of the products is a monochloropropane. Extension of their mechanism to the present situation would entail the formation of (16); abstraction from the methyl radical by the cyclopropyl radical would then lead to the observed monobromocyclopropane, together with methylene.[19] This mechanism is not in agreement with the trapping of a lithiobromide by D_2O or benzaldehyde, and indeed attempts to trap the methylene produced by addition of cyclo-octene were not successful. Not only was the monobromide (10) the only product when (5) was treated with MeLi (1 mol equiv.) at -60 °C and quenched at that temperature, but it was also obtained when the solution was refluxed for 15 min before quenching.* However, when the quenching was now carried out with ^2H_2O, no deuterium was incorporated into (10), and therefore (10) rather than (12; $R = Pr^i$) was present prior to quenching.

There appeared to be three possible sources of the proton needed to convert (12; $R = Pr^i$) into (10) in the reaction solution; absorbed moisture, the solvent, and the methyl bromide produced in the first step of the reaction. The first possibility was excluded by taking precautions to stop water being absorbed from the atmosphere; quenching by water absorbed on the glass-ware was excluded because no deuterium was incorporated in (10) when the reaction was carried out in a vessel that had been washed with D_2O prior to drying. Methyl bromide was excluded by addition of CD_3Br prior to work-up; again no deuterium was incorporated into (10). Furthermore, in order to exclude abstraction from methyl bromide held in some form of complex with the lithiobromide (12; $R = Pr^i$), (5) was treated with CD_3Li in ether at -60 °C and either quenched with H_2O at that temperature or warmed to 35 °C and then quenched. Again, isolated (10) contained no deuterium. This left one remaining possible source, the solvent (diethyl ether). Compound (5) in $[^2H_{10}]$diethyl ether was treated with MeLi in ordinary ether at -60 °C. Quenching at -60 °C gave (10) incorporating no

rather than deuteron abstraction, when allowance is made for the presence of both ether and $[^2H_{10}]$ether.

The internal protonation of (12; $R = Pr^i$) under these conditions apparently proceeds more readily than other reactions such as cyclopropylidene formation. It was thought that a change in reaction conditions might alter the course of the reaction. Treatment of (5) with MeLi (1.1 mol equiv.) at -60 °C in the presence of [18]crown-6 ether (0.1 mole quiv.), followed by refluxing, led only to the monobromide (10). Addition of hexamethyl-phosphoramide (1 mol equiv.) or triethylamine in place of the crown ether also caused little change in the product. However addition of ethereal MeLi (1.1 mol equiv.) to (5) in tetrahydrofuran at below -60 °C followed by quenching led to (10) as the major product, together with two isomeric bromomethyl compounds (17a) and (17b). The gross structure of these two products was established by dehydrobromination to (18) with $KOBu^t$–DMSO [87% based on (17a) and (17b)]; (17a) was assigned as the isomer with the CMeBr signal at lower field, *syn* to the amide linkage.[20-23] The formation of (17a) and (17b) is in keeping with the known
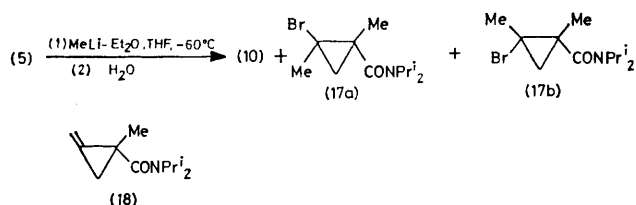
effect of tetrahydrofuran in increasing the rate of substitution of alkyl halides by alkyl-lithium reagents.[24] Presumably the lithiobromide (12; $R = Pr^i$) reacts rapidly in tetrahydrofuran with methyl bromide generated in its formation, to produce (17a). Tetrahydrofuran presumably also accelerates the rate of formation of the epimer of (12), and hence of (17b).

(ii) *Reaction of* (5) *with* MeLi (2.2 *mol equiv.*).—Reaction of (5) with MeLi (2.2 mol equiv.) at -60 °C followed by low-temperature quenching with H_2O has been stated to give the monobromide (10); if the solution was allowed to warm slowly to 35 °C and then quenched a complex mixture was obtained, which contained *inter alia* (11; $X = Me$), (19), (20), (10), (17a), and probably
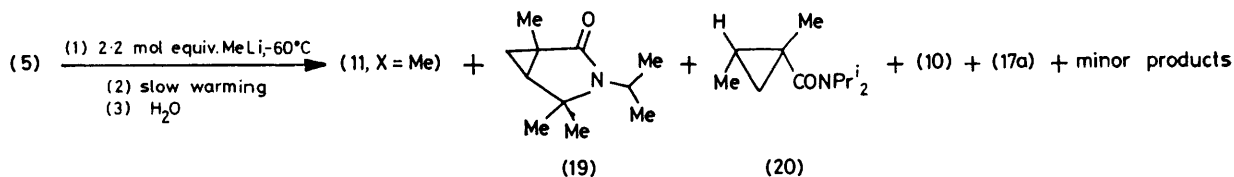
deuterium. However, when the solution was warmed to 35 °C for 5 min before quenching with H_2O, isolated (10) showed 16% incorporation of one deuterium atom. This corresponds to an isotope effect of *ca.* 3 for proton

* Reaction of (6) with 1.1 mol equiv. MeLi at -60° followed by refluxing and quenching with water also led to the corresponding monobromide (9).

(21). When the temperature was raised rapidly to 35 °C, or when (5) was treated with MeLi (1 mol equiv.) at -60 °C and the solution was then refluxed and treated rapidly with a second equiv. of MeLi, an 8 : 1 mixture of (20) and (19) was obtained (58%), together with a trace of (22). Quenching with D_2O led to no incorporation of deuterium into (20), suggesting that the latter arose by

a simple alkylation of (10), rather than by either a nucleophilic displacement on (12; R = Pr[i]) by MeLi,[25a] or alkylation of (12; R = Pr[i]) by bromomethane, followed by metal–halogen exchange. The stereochemistry of the secondary methyl group in (20) could be assigned from its chemical shift and also from the effect of solvent on this shift.[25b] However, to provide chemical proof, the amide (23) was prepared. Addition of dibromocarbene to methyl tiglate using the phase-transfer method [26] led to (24; X = OMe) which was hydrolysed to the acid (24; X = OH); conversion to the acid chloride, and reaction with di-isopropylamine produced (24; X = NPr[i]$_2$). Reduction of the latter with sodium–liquid ammonia led to (23), which was similar to, but nevertheless different from, (2). The addition of dichlorocarbene to methyl tiglate has been reported [13,27] to proceed in a cis-manner, though a Michael addition of CX_3^- followed by loss of X^- could lead to isomerisation. In order to exclude this possibility (24; X = NPr[i]$_2$) was treated with MeLi (1 mol equiv.) in ether, a reaction known to remove the halogen cis to the amide group (see above). As expected, the monobromide (25) was isolated in essentially quantitative yield, and the cis-relationship of the ring hydrogens was confirmed by their coupling constant.[28]

(21)

(22) R = Me
(23) R = H

(24)

(25)

(26)

(27) X = H, Y = Cl
(28) X = Cl, Y = H
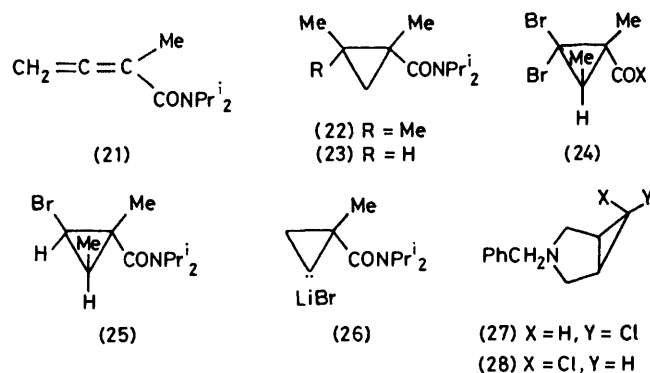
The yield of (19) could be considerably improved by treating (5) with MeLi (1.1 mol equiv.) at −60 °C, heating to 35 °C, and then very slowly adding a second equiv. of MeLi. Both the above results are consistent with a two-step reaction leading to either (19) or (20). Thus the dibromide (5) reacts with one equivalent of MeLi to give the lithiobromide (12; R = Pr[i]); this undergoes proton abstraction from the solvent to produce (10) faster than it undergoes loss of lithium bromide to produce (26). Compound (10) is then attacked by a second equiv. of MeLi to produce either (20) or (19); the relative importance of these routes is dependent on the MeLi concentration.

(iii) Reaction of (10) with MeLi.—Monobromocyclopropanes are known to react with butyl-lithium to produce lithiocyclopropanes and (presumably) butyl bromide; the lithiocyclopropanes are stereochemically stable and can be quenched by a variety of electrophiles.[29-34] The reaction of monobromocyclopropanes

with MeLi is not widely described. However, as suggested by the results of section (ii), (10) did indeed react with MeLi. Rapid addition of MeLi (1 mol equiv.) to a refluxing solution of (10) in ether caused complete reaction in 5 min. After quenching, two products, (20) and (19), were isolated in the ratio 8 : 1. The formation of (20) presumably occurs via lithium–halogen exchange to produce a lithiocyclopropane which is alkylated by the methyl bromide also produced. Analogous reactions have been reported for cyclopropyl iodides.[29,31]

The formation of (19) could proceed by initial metallation to give (12; R = Pr[i]) followed by loss of LiBr to produce (26) which inserts into the C–H bonds α to nitrogen. There are indeed two reports in the literature of reactions of monochlorocyclopropanes, e.g. (27), with BuLi leading to cyclopropylidene-derived products.[35] In both cases, (10) and (27), there is a nitrogen at the 4-position relative to the halogen; this presumably enhances the rate of metallation and/or cyclopropylidene formation. Indeed the isomeric chloride (28) gives no cyclopropylidene-derived products with BuLi. Initial experiments [36] have shown that while simple monobromocyclopanes such as the isomeric 9-bromobicyclo-[6.1.0]nonanes can react with MeLi to give cyclopropylidene-derived products, the reaction is extremely slow.*

What is most difficult to rationalise is the fact that the reactions of (5) and (10) with MeLi can both lead to the lithiobromocyclopropane (12; R = Pr[i]) but that this then reacts in two quite distinct fashions, either by proton abstraction from the solvent, or by cyclopropylidene formation. At first sight one may invoke a temperature effect to explain these results as most reactions of (5) were carried out at −60 °C whereas that of (10) occurred at 35 °C; the cleavage of ethers by an alkyl-lithium has in fact been reported to show a negative temperature effect, being slower at +25 than at −21 °C.[37] However, as stated earlier, addition of MeLi (1.1 mol equiv.) to (5) at 35 °C also leads to (10). One real difference between the two reactions is that treatment of (5) with MeLi leads to MeBr and (12; R = Pr[i]), whereas reaction of (10) with MeLi leads to methane and (12; R = Pr[i]). It is not impossible that the formation of these species in a reaction cage is affecting the further decomposition of (12; R = Pr[i]). It is also possible that the reaction of MeLi with a monobromide leads directly to a cyclopropylidene, while the reaction with a dibromocyclopropane leads initially to a lithiobromocyclopropane.

Further information concerning these processes was obtained from the reactions of (15) with MeLi. Treatment of (15) (78% $^2H_1$) with MeLi at −60 to −78 °C followed by quenching with water at low temperature led to quantitative recovery of (15) with essentially no change in the $^2H_1$-content. Clearly there is no formation of (12; R = Pr[i]) under these conditions. When

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* The reaction is more rapid in the presence of TMEDA, being complete in ca. 24 h at 35 °C in ether. TMEDA is known to dramatically increase the rate of metallation by alkyl-lithiums.[38]

the reaction was warmed to -20 °C for 5 min before quenching *ca.* 25% reaction was found to have occurred leading to a 1 : 4 mixture of (19) and (20); recovered starting material had a $^2H_1$ content of 76%. However, if the reaction was allowed to reach ambient temperature before immediate quenching with water, recovered (15) (*ca.* 70%) had a $^2H_1$ content of 95%, while the products, (20) and (19), were obtained with $^2H_1$ contents of 33 and 0%, respectively. The increased labelling of (15) presumably arises through an isotope effect; however a primary isotope effect would only occur in the formation of the minor product, (19), *via* the lithiocyclopropane (12), and a secondary isotope effect in the transformation of (10) to (20) must be invoked. The complete lack of $^2H_1$ in (19) is in agreement with the intermediacy of (12). If (15) (78% $^2H_1$) was treated with MeLi at -60 to -78 °C and then refluxed for 5 min before quenching, complete reaction of (15) [and the impurity, (10)] had occurred; (20) obtained in this case was found to be 40% $^2H_1$. It seems that the transformation of (10) or (15) to (20) proceeds to a considerable degree with retention of the cyclopropyl CHBr proton; there is, however, a second process which involves the removal of this proton.

Of particular importance is the fact that in none of these experiments is there any reduction in the ^2H content of recovered (5); there can therefore be no process of rapid metallation of (15) occurring to produce (12; R = Pr^i) which then more slowly forms (19).

EXPERIMENTAL

Except where stated otherwise reactions were conducted under dry, oxygen-free nitrogen in dry solvent, either in a semi-closed system by injection through a septum cap, or in a flowing system, and were stirred vigorously except when refluxing. Methyl-lithium was used as a solution in ether; its strength was determined by the diphenylacetic acid titration method.[39] Trideuteriobromomethane was prepared by the action of PBr$_3$ on [$^2H_4$]methanol; ethereal trideuteriomethyl-lithium (0.8M) was obtained by the reaction of excess of lithium with trideuteriomethyl bromide in ether. Organic extracts were dried with MgSO$_4$ before removal of the solvent at 14 mmHg.

Analytical and preparative g.l.c. was performed on a Varian 2400 instrument using a 12-ft, 10% SE30 on 60—80 Celite column which was temperature programmed at 8° min^{-1} from 150 to 200 °C, unless otherwise stated. N.m.r. spectra were obtained on Varian EM360 and Brücker Spectrospin instruments; mass spectra were run on an A.E.I. MS-9 spectrometer.

2,2-Dibromo-1-methylcyclopropanecarboxylic Acid (7).—Methyl methacrylate (35 g, 350 mmol), bromoform (168 g, 720 mmol), cetrimide (1 g), and aqueous sodium hydroxide (50 g, 1 250 mmol) in water (80 cm³) were stirred vigorously at 55—65 °C for 2.5 h, and then at 25 °C for 18 h. After washing with ether (2 × 100 ml), the aqueous layer was brought to pH 1, and extracted with ether (3 × 250 ml). Evaporation and recrystallisation from acetone gave the acid (7) (46 g, 50%).[9,12] Removal of the solvent from the organic layer before acidification gave only bromoform.

2,2-Dibromo-1-methylcyclopropanecarbonyl Chloride (8).—The acid (7) (19 g, 74 mmol) was stirred for 18 h in thionyl

chloride (20 cm³), protecting the solution from moisture. Following removal of excess of thionyl chloride at 14 mmHg, distillation afforded (8) (17.5 g, 86%), b.p. 58—60 °C at 0.4 mmHg, as a colourless oil, which slowly darkened on standing; δ(CCl$_4$) 1.8 (4 H, m, Me and CH) and 2.53 (1 H, d, J 8 Hz, CH); $\nu_{max.}$ (film), decomposed on plates; m/e 238 (0.4%), 239 (1), 240 (0.7), 241 (1.7), 242 (0.4), 243 (0.8), and 40 (base). This compound was characterised as its crystalline derivative (6).

NN-*Di-isopropyl-2,2-dibromo-1-methylcyclopropanecarboxamide* (5).—Di-isopropylamine (4 cm³) was added cautiously to (8) (2.8 g, 10 mmol) in carbon tetrachloride (20 cm³). After the slurry had been refluxed for 0.5 h and cooled, it was diluted with dichloromethane (50 cm³) and washed successively with water (50 cm³), dilute sulphuric acid (1M, 50 cm³), and aqueous sodium hydroxide (1M, 50 cm³). The solution was evaporated to yield the *amide* (5) (2.7 g, 80%) as a viscous, chromatographically homogeneous, dark oil which could not be distilled: δ(CCl$_4$; 296 K) 1.2—1.6 (16 H, m, 5 Me and ring CH), 2.28 (1 H, d, J 7.6 Hz, ring CH), and 3.36 and 4.06 (each 1 H, sept., J 7.0 Hz, 2 C*H*Me$_2$); $\nu_{max.}$ (film) 690, 1 040, 1 340, 1 375, 1 445, 1 645, and 2 930 cm^{-1} (Found: M^+ 338.984 3. $C_{11}H_{19}Br_2NO$ requires M, 338.983 4); m/e 339 (17%), 341 (35), 343 (16), and 43 (base).

NN-*Dimethyl-2,2-dibromo-1-methylcyclopropanecarboxamide* (6).—A 25% solution of dimethylamine in carbon tetrachloride (25 cm³) was added to (8) (5 g, 18 mmol) in carbon tetrachloride (10 cm³) and the slurry was refluxed for 0.5 h. After cooling, the solution was diluted with dichloromethane (50 cm³), washed with saturated aqueous NaHCO$_3$ (50 cm³), and evaporated to yield the *dimethylamide* (6) (3.6 g, 67%), m.p. 84—86 °C (from H$_2$O); δ(CCl$_4$) 1.48 (1 H, d, J 7.5 Hz, ring CH), 1.52 (3 H, s, ring Me), 2.23 (1 H, d, J 7.5 Hz, ring CH), and 2.92 and 3.14 (each 3 H, s, NMe$_2$); $\nu_{max.}$ (KBr) 690, 710, 765, 1 130, 1 270, 1 405, 1 645, and 2 900 cm^{-1} (Found: C, 29.45; H, 3.75; N, 4.85; $C_7H_{11}Br_2NO$ requires C, 29.7; H, 3.9; N, 4.95%); m/e 282 (0.3%), 283 (5.0), 284 (1.1), 285 (9.7), 286 (1.4), 287 (5.1), 288 (0.5), 176 (base), and 178 (99).

(E)-NN-*Dimethyl-2-bromo-1-methylcyclopropanecarboxamide* (9).—(*a*) Methyl-lithium (1.7 cm³, 1.1M) was added during 30 s to a stirred slurry of (6) (0.5 g, 1.75 mmol) in ether (5 cm³) at -60 to -78 °C. After 45 min the solution was brought to room temperature, quenched with water, washed with water (5 cm³), and evaporated to leave (9) as an almost pure liquid. Chromatography over silica gel, with chloroform as eluant, afforded pure (9) (0.32 g; 89%); δ(CCl$_4$) 0.81 (1 H, dd, J_{AB} 6.4, J_{AX} 4.2 Hz, H$_A$), 1.38 (3 H, s, 1-Me), 1.59 (1 H, dd, J_{AB} 6.4, J_{BX} 7.8 Hz, H$_B$), 2.92 (6 H, br s, NMe$_2$), and 3.18 (1 H, dd, J_{AX} 4.2, J_{BX} 7.8 Hz, H$_X$); $\nu_{max.}$ (film) 1 035, 1 410, 1 645, and 2 900 cm^{-1} (Found: M^+, 205.009 5. $C_7H_{12}BrNO$ requires M, 205.010 2); m/e 204 (3%), 205 (24), 206 (5), 207 (24), 208 (3), and 72 (base).

(*b*) Reaction as above (half scale), but quenching at below -60 °C, afforded (9) (0.174 g; 97%) (n.m.r. and g.l.c.).

Reaction of the Amide (6) *with Methyl-lithium* (2 mol *equiv.*).—Methyl-lithium (1.8 cm³, 1.1M) was added to a slurry of (6) (0.500 g, 1.77 mmol) in ether (10 cm³), at -60 to -78 °C. After 5 min, the solution was rapidly brought to reflux, and further methyl-lithium (1.8 cm³, 1.1M) in ether (2 cm³) was added dropwise. Work-up as above gave (11; X = Me) (0.271 g) (n.m.r.).

Correlation of the Configuration of (9) *and* (11; X = OH).—Methyl-lithium (2 cm³, 1.1M) was added to (9) (0.300 g,

1.46 mmol) in ether (5 cm³). After 10 min, the reaction was quenched cautiously with water. Work-up as above led to (11; X = Me) (0.219 g, 95%), pure by g.l.c. This material was degraded by the iodoform reaction [40] to (11; X = OH) (0.086 g, 36%) identical to authentic material by n.m.r. and mass spectrometry.[9]

(E)-NN-*Di-isopropyl-2-bromo-*1-*methylcyclopropanecarboxamide* (10).—(a) Methyl-lithium (5 cm³, 1.3M) was added to (5) (2 g, 5.9 mmol) in ether (20 cm³) at −60 to −78 °C. After 5 min the reaction was quenched at below −60 °C by addition of water, brought to room temperature, and worked up as above to produce (10) (1.38 g, 90%), as an almost pure liquid. Distillation gave compound (10) (0.920 g, 60%), b.p. 78—80 °C at 0.1 mmHg; δ(CDCl₃; 255 K) 0.89 (1 H, dd, J_{AX} 5.0, J_{AB} 6.8 Hz, H$_A$), 1.13—1.54 (15 H, m, 5 Me), 1.71 (1 H, dd, J_{BX} 8.0, J_{AB} 6.8 Hz, H$_B$), 3.17 (1 H, dd, J_{AX} 5.0, J_{BX} 8.0 Hz, H$_X$), and 3.55 and 4.25 (each 1 H, sept., J 6.5 Hz, isopropyl CH); $\nu_{max.}$ (film) 1 045, 1 350, 1 380, 1 450, 1 640, and 2 950 cm⁻¹, (Found: M^+, 261.075 5. $C_{11}H_{20}BrNO$ requires M, 261.072 8); m/e 261 (14%), 263 (15), and 161 (base).

(b) Methyl-lithium (2.5 cm³, 1.3M) was added during 30 s, to (5) (0.500 g, 1.47 mmol) in ether (5 cm³) at −60 to −78 °C. After 15 min the reaction was quenched by the cautious addition of water at −60 °C and the products were warmed to 25 °C and extracted as above to give (10) (0.35 g).

(c) Compound (5) was treated as in (a) except that the crude products were raised to reflux temperature for 15 min before quenching. Work-up as above led to (10) (0.339 g, 88%) as the only major product.

(d) Methyl-lithium (1.3 cm³, 1.3M) was added dropwise to (5) (0.5 g, 1.47 mmol) in ether (5 cm³) at −60 to −78 °C. After 5 min the reaction was quenched by dropwise addition of ²H₂O as in (b) and worked up to give a mixture of (15) and (10) (0.350 g, 92%). Preparative g.l.c. afforded (15), which (mass spectrometry) was contaminated with 37% (10); δ(CCl₄; 296 K) 0.83 (1 H, m, CH), 1.3 (12 H, m, 4 Me), 1.42 (3 H, s, ring Me), 1.67 (1 H, m, ring CH), 3.16 (0.3 H, dd, J 5.0 and 8.0 Hz, ring CH), and 3.33 and 4.22 (each 1 H, m, isopropyl CH); $\nu_{max.}$ (film) 1 050, 1 215, 1 350, 1 380, 1 450, 1 645, 2 310 (weak), and 2 930 cm⁻¹.

(e) Two flasks (20 cm³) one containing ²H₂O (10 cm³) and the other H₂O were each heated to reflux the contents. After 18 h the contents were poured out and the flasks dried at 110 °C for 5 h. A reaction as in (a) above (1/8 scale) was carried out in each flask, leading to (10) (0.17 g) in each case. The products were purified by g.l.c. and were found to be identical by mass spectrometry.

(f) Methyl-lithium (1.5 cm³, 1.1M) was added to (5) (0.5 g, 1.47 mmol) in ether (7.5 cm³) at −60 to −78 °C. After 30 s, 30 min, and 120 min, aliquots (3 cm³) were removed and quenched rapidly with ²H₂O. Work-up gave a mixture of (15) and (10) as the only product (>95%) in each case. Each sample was purified by g.l.c. and analysed by mass spectrometry to ascertain the deuterium content. In all three cases the result (±1%) was 25% non-deuteriated, 75% mono-deuteriated.

(g) To (5) (0.25 g, 0.83 mmol) in ether (3.25 cm³) under dry N₂ in a closed system, at −60 to −78 °C, was added methyl-lithium (0.75 cm³, 1.3M). After 5 min the solution was refluxed for 20 min and quenched with ²H₂O. G.l.c. after work-up indicated that the product was (10) (>95%). Following preparative g.l.c., n.m.r. analysis showed >95% non-deuteriated product which was confirmed by mass spectrometry (non-deuteriated 95%, mono-deuteriated 5%).

(h) In the presence of ²H₃CBr. Methyl-lithium (0.75 cm³, 1.1M) was added to (5) (0.250 g, 0.73 mmol) in ether (5 cm³) at −60 to −78 °C; bromotrideuteriomethane (0.5 cm³) was then added. The reaction mixture was warmed to −40 °C for 30 min, quenched with water, and worked up as before to yield (10) (0.175 g, 88%) (g.l.c.). Following preparative g.l.c., mass spectrometry indicated >95% non-deuteriated product.

(i) In the presence of deuteriated ether (high-temperature quench). Methyl-lithium (0.23 cm³, 0.7M) was added to (5) (0.050 g, 0.14 mmol) in [²H₁₀]diethyl ether (0.7 cm³) at −60 to −78 °C. After 5 min, the solution was rapidly warmed to room temperature and after a further 5 min was quenched with water; work-up gave an oil (0.035 g), which by g.l.c. was essentially only (10). Following preparative g.l.c., mass spectrometry showed 84% non-deuteriated and 16% mono-deuteriated product.

(j) In the presence of deuteriated ether (low-temperature quench). Repetition of the above procedure, but quenching below −60 °C after 15 min, afforded (10), 92% non-deuteriated and 8% mono-deuteriated product by mass-spectrometry.

Attempted Hydrolysis of (10).—The monobromide (10) (0.130 g, 0.5 mmol), methanol (5 cm³), and dilute hydrochloric acid (1M, 2 cm³) were stirred together for 18 h. Work-up as before gave only (10) (0.123 g, 95%).

The monobromide (10) (0.130 g, 0.5 mmol), methanol (5 cm³) and aqueous sodium hydroxide (1M, 2 cm³) were stirred for 18 h. Following acidification (dilute hydrochloric acid, 1M, 2 cm³) work-up again gave (10) (0.120 g, 92%).

Attempted Trapping of the Lithiobromide (12; R = Pr^i).— (a) Methyl-lithium (0.7 cm³, 1.1M) was added to (5) (0.25 g, 0.73 mmol) in ether (3 cm³) at −60 to −78 °C. After 2 min, small pieces of solid carbon dioxide (ca. 1 g) were added. After 10 min, the reaction was quenched by the addition of water, followed by dilute hydrochloric acid (1M, 5 cm³), extracted with chloroform (10 cm³), and evaporated to afford a crude oil (0.180 g) consisting mainly of the monobromide (10). Addition of excess of ethereal diazomethane afforded no evidence for an acidic product.

(b) Methyl-lithium (0.7 cm³, 1.1M) was added to (5) (0.25 g, 0.73 mmol) in ether (3 cm³) at −60 to −78 °C. After 2 min, trimethylsilyl chloride (0.3 cm³) was added, and the solution was warmed to reflux temperature and maintained there for 1 h. Quenching with water and work-up as before gave an oil (0.180 g); this was a mixture of two products (ca. 10 : 1 by g.l.c.), which following preparative g.l.c. were shown to be (10) and (5) respectively.

(c) Methyl-lithium (1.4 cm³, 1.1M) was added to (5) (0.5 g, 1.46 mmol) in dry ether (5 cm³) at −60 to −78 °C; the products were treated with allyl bromide (0.5 cm³). The reaction mixture was allowed to warm to −10 °C during 15 min and then quenched with water. Work-up gave (10) (0.340 g, 88%).

(d) Repetition of the above procedure, substituting iodomethane (0.5 cm³) for allyl bromide, again afforded (10) (0.340 g, 88%).

NN-*Di-isopropyl-2-bromo-2-*(α-*hydroxybenzyl*)-1-*methyl-cyclopropanecarboxamide* (14).—Methyl-lithium (1M, 1.6 cm³) was added during 30 s to (5) (0.500 g, 1.47 mmol) in ether (5 cm³) at −60 to −78 °C. After 2 min, benzaldehyde (0.170 g, 1.6 mmol) in ether (1 cm³) was added dropwise. After a further 5 min, the temperature was raised to 25 °C and water (10 cm³) was added. Work-up gave a partially

crystalline residue. Chromatography over silica gel (20 g) with chloroform as eluant, afforded (i) benzaldehyde, (ii) a mixture of (10) and a compound tentatively identified as a diastereoisomer of (14), (iii) almost pure (10) (0.051 g), and finally (iv) the *hydroxybenzyl derivative* (14) (0.170 g). Recrystallisation from carbon tetrachloride afforded (14) (0.052 g), m.p. 152—154 °C; δ(CDCl₃) 1.0—1.5 (13 H, m, Prⁱ-Me and ring CH), 1.60 (3 H, s, ring Me), 2.10 (1 H, d, *J* 6.4 Hz, ring CH), 3.33 and 4.29 (each 1 H, sept., *J* 6.8 Hz, isopropyl CH), 3.9 (1 H, br, OH), 5.26 (1 H, d, *J* 6.8 Hz, Ph-C*H*), and 7.1—7.4 (5 H, m, aromatic H) (addition of D₂O caused the signal at δ 3.9 to disappear and that at 5.26 to collapse to a singlet. Irradiation at δ 1.1 caused the signal at 2.10 to collapse to a singlet. Irradiation at δ 3.33 caused the higher-field portion of the δ 1.0—1.5 multiplet to sinplify, and irradiation at δ 4.21 simplified the lower-field portion); ν$_{max.}$ (KBr) 705, 775, 1 020, 1 355, 1 450, 1 470, 1 625, 2 900, 2 930, 3 040, and 3 340 cm⁻¹ (Found: C, 58.75; H, 7.15; N, 3.80. C₁₈H₂₆BrNO₂ requires C, 58.8; H, 7.1; N, 3.8%).

Reaction of the Amide (5) *with* MeLi *in the Presence of Hexamethylphosphoramide, Dibenzo*[18]*crown*-6, *or Tri-ethylamine.*—(*a*) Methyl-lithium (1.5 cm³, 1.1M) was added to (5) (0.250 g, 0.73 mmol) and hexamethylphosphoramide (0.5 cm³) in ether (2.5 cm³) at −60 to −78 °C. On warming to room temperature, g.l.c. indicated that (12), (20), and (16) were formed in approximately equal proportions.

(*b*) Methyl-lithium (0.85 cm³, 1.1M) was added to (5) (0.250 g, 0.73 mmol) in ether (2.5 cm³) containing tri-ethylamine (10 μl, 0.07 mmol), at −60 to −78 °C. The solution was raised to reflux, g.l.c. indicating that (10) was the only product. A further mol equiv. of methyl-lithium was added when g.l.c. indicated that (11; X = Me), (19), and (20) (*ca.* 1 : 1 : 2) were formed.

(*c*) To (5) (0.250 g, 0.73 mmol) and dibenzo[18]crown-6 (0.053 g, 0.147 mmol) in ether (2.5 cm³), at −60 to −78 °C, was added methyl-lithium (1.5 cm³). G.l.c. indicated that (10) was the only product. The solution was allowed to slowly warm to room temperature, when g.l.c. indicated that (11; X = Me), (19), and (20) (*ca.* 1 : 1 : 3) were formed.

(Z)- *and* (E)-NN-*Di-isopropyl*-2-*bromo*-1,2-*dimethyl-cyclopropanecarboxamide* (17a) *and* (17b).—Methyl-lithium (3 cm³, 1.1M) was added to (5) (1 g, 2.94 mmol) in tetra-hydrofuran (10 cm³) at −60 to −78 °C. The solution was stirred for 5 min at below −60 °C and then cautiously quenched with water. Work-up gave (10), (17a), and (17b) (total 0.617 g) (*ca.* 3 : 1 : 2 by g.l.c., 12-ft, 10% SE30 on 60—80 Celite column, 170 °C). The products were sepa-rated by g.l.c. to yield in order of elution: (10); (Z)-(17a); δ(CCl₄) 0.85 (1 H, d, *J* 6.5 Hz, CH), 1.16—1.55 (16 H, m, 5 Me and ring CH), 1.69 (3 H, s, 2-Me), and 3.19 and 3.96 (each 1 H, sept., *J* 6.5 Hz, isopropyl CH); ν$_{max.}$ (film) 1 045, 1 140, 1 350, 1 380, 1 450, 1 640, and 2 930 cm⁻¹ (Found: *M*⁺, 275.088 0. C₁₂H₂₂BrNO requires *M*, 275.088 5); *m/e* 275 (12%), 277 (12), and 196 (base); and finally (*E*)-(17b); δ(CCl₄) 0.69 (1 H, d, *J* 6.6 Hz, ring CH), 1.6—1.55 (16 H, m, 5 Me and ring CH), 1.85 (3 H, s, 2-Me), and 3.23 and 4.02 (each 1 H, sept., *J* 6.8 Hz, isopropyl CH); ν$_{max.}$ (film) 1 045, 1 215, 1 320, 1 375, 1 445, 1 640, and 2 930 cm⁻¹ (Found: *M*⁺, 275.089 9. C₁₂H₂₂BrNO requires *M*, 275.088 5); *m/e* 275 (11%); 277 (10), and 196 (base).

NN-*Di-isopropyl*-1-*methyl*-2-*methylenecyclopropanecarbox-amide* (18).—To a solution of the mixture of (10), (17a), and (17b) [(10) : (17a) + (17b) ,1 : 1 by g.l.c.] in dry dimethyl sulphoxide (5 cm³) was added potassium t-but-

oxide (1 g). After 18 h the solution was diluted with brine and extracted with ether. Work-up gave an oil (0.132 g). By g.l.c. this was mainly one product, which was collected to yield *compound* (18) (0.072 g, 87%, based on methyl-bromides); δ(CCl₄) 0.97 (1 H, m, ring CH), 1.23 and 1.32 (each 6 H, d, *J* 6 Hz, isopropyl Me), 1.35 (3 H, s, ring Me), 1.64 (1 H, m, ring CH), 3.90 (2 H, m, C*H*Me₂), 5.32 (1 H, m, olefinic CH), and 5.37 (1 H, m, olefinic CH) (irradiation at δ 1.64 caused the signals at 5.32 and 7.37 to sharpen); ν$_{max.}$ (film) 900, 1 050, 1 220, 1 340, 1 380, 1 450, and 2 930 cm⁻¹ (Found: *M*⁺, 195.162 0. C₁₂H₂₁NO requires *M*, 195.162 3), *m/e* 195 (11%) and 67 (base).

Reaction of (5) *with Methyl-lithium* (2.2 *equiv*.).—(*a*) *Slow warming from* −60 *to* +35 °C. Methyl-lithium (3.0 ml, 1.1M) was added to (5) (0.5 g, 1.47 mmol) in ether (5 cm³) at −60 to −78 °C. After 5 min, the solution was allowed to warm slowly to room temperature, and then refluxed for 10 min. Quenching with water and work-up as before led to a complex mixture. G.l.c. indicated seven products, of which five were identified; in order of elution they were: (11; X = Me) (11 mg, 4%); an unidentified product (9 mg); (19) (40 mg, 15%); (20) (96 mg, 34%); an unidentified product (4 mg); (10) (19 mg, 5%); and (17a) (16 mg, 4%). A minor peak (*ca.* 0.05 of the second peak) wds eluted after the seventh peak, and was possibly the isomeric bromide (17b).

(*b*) *Rapid warming*. Methyl-lithium (2.5 cm³, 1.3M) was added to (5) (0.5 g, 1.47 mmol) in ether (5 cm³) at −60 to −78 °C. The solution was rapidly raised to reflux, held there for 5 min, and then quenched with water. Work-up gave a mixture of (20) and (19) (*ca.* 8 : 1 by g.l.c.). Pre-parative g.l.c. afforded (20) (0.147 g, 52%); δ(CCl₄; 296 K) 1.05 (2 H, m, CH₂), 1.15—1.5 (18 H, m, 6 Me), 1.86 (1 H, m, CH), 3.35 and 4.35 (each 1 H, m, C*H*Me₂); ν$_{max.}$ (film) 1 045, 1 215, 1 270, 1 350, 1 375, 1 445, 1 635, and 2 930 cm⁻¹ (Found: *M*⁺, 197.177 0. C₁₂H₂₃NO requires *M*, 197.178 0); *m/e* 197 (44%), 198 (7), and 154 (base). NN-*Di-isopropyl*-1,2,2-*trimethylcyclopropanecarboxamide* (22) was isolated as a minor product (0.012 g, 4%) having a slightly longer reten-tion time than (20); δ(CCl₄; *ca.* 300 K) 0.13 (2 H, m, CH₂), 0.9—1.6 (21 H, m, 7 Me), and 3.22 and 4.08 (each 1 H, m, C*H*Me₂); ν$_{max.}$ (film) 1 050, 1 120, 1 330, 1 375, 1 440, 1 630, and 2 920 cm⁻¹ (Found: *M*⁺, 211.193 0. C₁₃H₂₅NO requires *M*, 211.193 6); *m/e* 211 (26%) and 168 (base).

(*c*) *Attempted preparation of* [2-²H]-(20). Methyl-lithium (1.5 cm³, 1.1M) was added to (5) (0.25 g, 0.83 mmol) in ether (2.5 cm³) at −60 to −78 °C. After 5 min, the solution was warmed rapidly to reflux temperature, and after 10 min was quenched with ²H₂O. Work-up gave (20), and pre-parative g.l.c. and mass spectrometry indicated 95% non-deuteriated; 5% mono-deuteriated.

(*d*) *Dropwise addition of* MeLi. Methyl-lithium (1.3 cm³, 1.3M) was added to (5) (0.5 g, 1.47 mmol) in ether (5 cm³), at −60 to −78 °C. The solution was brought rapidly to reflux and further methyl-lithium (1.3 cm³) in ether (2 cm³), was added during 15 min. Quenching and work-up as before afforded a mixture of four products. Preparative g.l.c. gave: (i) (11; X = Me) (0.044 g, 17%), (ii) an un-identified product (0.028 g); (iii) the *lactam* (19) (0.114 g; 43%); δ(CCl₄) 0.54 (1 H, t, *J*$_{AX}$ 4.2, *J*$_{AB}$ 4.2 Hz, H$_A$), 0.62 (1 H, dd, *J*$_{BX}$ 7.2, *J*$_{AB}$ 4.2 Hz, H$_B$), 1.14 (3 H, s, 4-Me), 1.19 and 1.37 (6 H, each d, *J* 7.0 Hz, CH*Me₂*), 1.27 (6 H, s, 4- and 1-Me), 1.33 (1 H, partially obscured m, H$_X$), and 3.08 (1 H, sept., *J* 7.0 Hz, C*H*Me₂); ν$_{max.}$ (film) 1 360, 1 430, 1 680, and 2 930 cm⁻¹ (Found: *M*⁺, 181.146 6. C₁₁H₁₉NO

requires M, 181.146 7); m/e 181 (21%) and 166 (base); and (iv) (20) (0.027 g, 14%).

(e) *Reaction of the amide* (5) *with ethereal* MeLi (2 *mol equiv.*) *at reflux.* To a refluxing solution of (5) (0.500 g, 1.47 mmol) in ether (10 cm³) was added, dropwise, methyl-lithium (1.5 cm³, 1.1M) in ether (1 cm³). A portion was removed and quenched with water; g.l.c. analysis showed (19), (20), (10), and (5) (*ca.* 5 : 1 : 93 : 1). A further aliquot of methyl-lithium (1.3 cm³, 1.1M) in ether (1 cm³) was added dropwise. Work-up gave (11; X = Me), (19), (20), and (10) (n.m.r. and g.l.c. analysis: *ca.* 1 : 20 : 40 : 1).

Reaction of Amide (5) *with* ²H₃CLi.—(a) Ethereal trideuteriomethyl-lithium (1.2 cm³, 0.8M) was added to (5) (0.250 g, 0.73 mmol) in ether (5 cm³) at −60 to −78 °C. After 5 min, the solution was warmed to room temperature, and after a further 15 min it was quenched with water; work-up gave (10) (0.178 g, 88%). Following preparative g.l.c., mass spectrometry indicated >95% non-deuteriated product.

(b) Repetition of the above procedure, but holding the reaction at −60 to −78 °C for 1 h, and quenching at that temperature, afforded (10) (0.171 g, 87%) (g.l.c.). Following preparative g.l.c., mass spectrometry indicated >95% non-deuteriated product.

(c) Repetition of procedure (a), but using 2.4 cm³ of the alkyl-lithium, afforded (19) and (20) (0.152 g) (g.l.c. ratio *ca.* 1 : 3). Following preparative g.l.c., (19) was shown to be >95% non-deuteriated; (20) was >95% trideuteriated, <5% tetradeuteriated.

(d) Repetition of procedure (a) but using 1.5 cm³ of the alkyl-lithium afforded (10), (19), and (20) (0.165 g) (g.l.c. ratio *ca.* 10 : 1 : 3). Following preparative g.l.c., mass spectrometry indicated (10) was >95% non-deuteriated; (20) was >95% trideuteriated, <5%, tetradeuteriated.

Reaction of Methyl Tiglate with Dibromocarbene.—Methyl tiglate (8 g, 70 mmol), bromoform (35.5 g, 140 mmol), cetrimide (0.2 g), and sodium hydroxide solution [8.5 g, 210 mmol in water (20 cm³)] were stirred vigorously, and heated to 50 °C for 18 h. The reaction mixture was diluted with water (200 cm³), then extracted with ether (3 × 400 cm³). Evaporation gave an oil (23 g). Distillation afforded bromoform (10 g), followed by (E)-2,2-*dibromo*-1,3-*dimethyl*-1-*methoxycarbonylcyclopropane* (24; X = OMe) (12.1 g, 61%), b.p. 75—77 °C at 0.1 mmHg; δ(CCl₄) 1.18 (3 H, d, *J* 6.8 Hz, Me), 1.36 (3 H, s, Me), 2.36 (1 H, q, *J* 6.8 Hz, C*H*Me), and 3.75 (3 H, s, CO₂Me); ν_max. (film) 1 170, 1 280, 1 400, 1 635, and 2 930 cm⁻¹ (Found: C, 29.1; H, 3.2. C₇H₁₀O₂Br₂ requires C, 29.4; H, 3.5%).

The aqueous layer was acidified to pH 1, and re-extracted with chloroform (2 × 200 cm³). The organic extract was evaporated to yield a mixture of an unsaturated acid and the adduct (24; X = OH) (4.1 g). These were separated by conversion to the acid chlorides (see later) and fractional distillation. The unsaturated acid chloride fraction was reacted with methanol, and the resulting ester shown to be identical to authentic methyl tiglate. The acid chloride (24; X = Cl) (2.7 g) was slightly contaminated with tigloyl chloride.

Hydrolysis of the Ester (24; X = OMe).—The ester (24; X = OMe) (11.5 g, 40 mmol) was hydrolysed in aqueous ethanolic sodium hydroxide (H₂O, 50 cm³; EtOH, 150 cm³; NaOH, 8 g, 200 mmol) by stirring at room temperature for 18 h. After diluting with water (150 cm³), the solution was washed with ether (2 × 300 cm³); evaporation of the ethereal layer left no product. The aqueous extract was acidified

to pH 1 and extracted with chloroform (2 × 200 cm³). The organic extract was evaporated to yield (24; X = OH) as a crystalline solid (10.2 g, 95%). This acid, whilst highly crystalline, resisted attempts at recrystallisation, but was sufficiently pure for use in the next stage; a portion (0.3 g) was dissolved in ether (3 cm³) and t-butylamine (0.5 cm³) was cautiously added (**CAUTION**; a highly exothermic reaction occurred). Following evaporation of the remaining ether and excess of t-butylamine, the salt was readily recrystallised: m.p. 166—168 °C (from EtOH), δ([²H₆]DMSO) 1.05 (3 H, s, *J* 6.2 Hz, CH*Me*), 1.20 (3 H, s, Me), 1.26 (9 H, s, Buᵗ), 2.21 (1 H, q, *J* 6.2 Hz, C*H*Me), and 8.0 (3 H, br, NH₃⁺) (addition of deuterium oxide caused the signal at δ 8.0 to disappear); ν_max. (KBr) 735, 850, 910, 960, 1 360, 1 395, 1 560, 1 635, 2 230, 2 520, 2 600, 2 710, 2 770, 2 870, and 2 920 cm⁻¹ (Found: C, 35.1; H, 5.55; N, 4.05. C₁₀H₁₉Br₂NO₂ requires C, 35.1; H, 5.5; N, 4.1%).

NN-*Di-isopropyl-2,2-dibromo-1,3-Dimethylcyclopropane-carboxamide* (24; X = NPrⁱ₂).—The acid (24; X = OH) (9.5 g, 35 mmol) was dissolved in thionyl chloride (20 cm³). After 18 h, excess of thionyl chloride was removed at 14 mmHg, and the product was distilled to yield (24; Y = Cl) (9.6 g, 95%), b.p. 73—75 °C at 0.5 mmHg; δ(CCl₄) 1.25 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.55 (3 H, s, Me), and 2.43 (1 H, q, *J* 6.5 Hz, C*H*Me). The acid chloride was dissolved in carbon tetrachloride (50 cm³) and di-isopropylamine (15 cm³) added cautiously. After refluxing for 2 h, the slurry was diluted with dichloromethane (100 cm³), and washed with sodium hydroxide solution (3M, 100 cm³) and water (100 cm³). The organic extract was evaporated to yield the *amide* (24; X = NPrⁱ₂) (10.2 g, 87%) as a chromatographically homogeneous, partially crystalline oil; δ(CCl₄) 1.1—1.5 (18 H, m, 6 Me), 2.18 (1 H, q, *J* 6.5 Hz, C*H*Me), and 3.36 and 4.00 (each 1 H, sept., *J* 6.5 Hz, 2 C*H*Me₂); ν_max. (film) 735, 1 040, 1 350, 1 640, and 2 930 cm⁻¹ (Found: *M*⁺, 352.998 3. C₁₂H₂₁Br₂NO requires *M*, 352.999 0); *m/e* 353 (6%), 355 (12), 357 (6), and 43 (base).

NN-*Di-isopropyl-1,2-dimethylcyclopropanecarboxamide* (23).—The amide (24; X = NPrⁱ₂) (2.76 g, 7.8 mmol) in ether (10 cm³) was added during 2 min to sodium (0.72 g, 31 mmol) in liquid ammonia (50 cm³). After a further 2 min, ammonium chloride (5 g) and then ethanol (10 cm³) were added. The reaction mixture was diluted with ether (50 cm³), washed with water (500 cm³), evaporated, and distilled to yield (23), b.p. 58—60 °C at 0.4 mmHg (0.93 g, 61%); δ(CCl₄) 0.8—1.4 (21 H, m, 6 Me, C*H*Me, and CH₂), and 3.7 (2 H, br, 2 C*H*Me₂); ν_max. (film) 1 040, 1 210, 1 330, 1 375, 1 440, 1 645, and 2 940 cm⁻¹ (Found: *M*⁺, 197.178 3. C₁₂H₂₃NO requires *M*, 197.178 0); *m/e* 197 (11%) and 97 (base).

NN-*Di-isopropyl-2-bromo-1,3-dimethylcyclopropane-carboxamide* (25).—Methyl-lithium (1M, 1.6 cm³) was added during 30 s to (24; X = NPrⁱ₂) (0.500 g, 1.42 mmol) in ether (5 cm³) at −60 to −78 °C. Work-up as before gave an oil (0.356 g), which was >95% one component by g.l.c. Preparative g.l.c. afforded pure *compound* (25); δ(CCl₄) 1.0—1.5 (19 H, m, 6 Me and C*H*Me), 3.25 (1 H, d, *J* 7.6 Hz, C*H*Br), and 3.6 (2 H, m, 2 C*H*Me₂); ν_max. (film) 685, 1 045, 1 335, 1 380, 1 450, 1 645, and 2 940 cm⁻¹ (Found: *M*⁺, 275.086 7. C₁₂H₂₂BrNO requires *M*, 275.088 5); *m/e* 275 (50%), 276 (21), 277 (45), 278 (20), and 196 (base).

Reaction of the Monobromide (10) *with Ethereal Methyllithium.*—Methyl-lithium (1.6 cm³, 1.1M) in ether (2 cm³) was added dropwise to a refluxing solution of (10) (0.400 g, 1.53 mmol) in ether (10 cm³). Quenching with water

followed by work-up as before gave (19) and (20) (0.225 g) (n.m.r. and g.l.c. showed a ratio of *ca.* 3 : 1).

The above was repeated adding the MeLi over 10 s. Work-up gave an oil (0.230 g) which was (19) and (20) by g.l.c. (ratio *ca.* 4 : 1).

Reaction of Deuteriated Monobromide (15) *with Methyllithium.*—Throughout this series of experiments a (10)–(15) mixture (22 : 78 by mass spectrometry) was used.

(*a*) Methyl-lithium (0.85 cm³, 1M) was added to (10/15) (0.200 g, 0.77 mmol) in ether (2.5 cm³) at −60 to −78 °C. After 5 min, the reaction was quenched by the cautious addition of water. Following warming to room temperature, work-up gave (15) (0.195 g, 98%) (g.l.c.). Following preparative g.l.c., mass spectrometry showed a (10) : (15) ratio of 24 : 76.

(*b*) Repetition of the foregoing procedure, but warming to −20 °C for 5 min before quenching, afforded (10), (20), and (19) (g.l.c. ratio *ca.* 12 : 1 : 4). Following preparative g.l.c., mass spectrometry showed a (10) : (15) ratio of 24 : 76.

(*c*) Repetition of the foregoing procedure, but warming to room temperature, followed by immediate quenching, afforded (10), (20), and (19) (g.l.c. ratio *ca.* 18 : 1 : 5). Following preparative g.l.c., mass spectrometry showed the (10):(15) ratio to be 5 : 95; the ratio of non-deuteriated to mono-deuteriated product for (20) was 67 : 33, and for (19) 98 : 2.

(*d*) Repetition of the foregoing procedure, but refluxing the solution for 5 min afforded (20) and (19) (g.l.c. ratio *ca.* 1 : 4). Following preparative g.l.c., mass-spectrometry showed (20) to be 60% non-deuteriated and 40% mono-deuteriated.

(*e*) Repetition of (*d*) afforded (20) which was 55% non-deuteriated and 45% mono-deuteriated.

Reaction of (5) *with Methyl-lithium in the Presence of Cyclo-octene.*—Methyl-lithium (1.5 cm³, 1.1M) was added to (5) (0.419 g, 1.38 mmol) and cyclo-octene (0.468 g, 4.26 mmol) in ether (10 cm³), at −60 to −78 °C. After 25 min, the solution was refluxed for 30 min. Aliquots were periodically removed and analysed by g.l.c. Work-up as before gave an oil; n.m.r. indicated the presence of (10) and cyclo-octene. G.l.c. analysis did not indicate the presence of any bicyclo[6.1.0]nonane.

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