

The Preparation of *exo*- and *endo*-6-Bromo-3-oxabicyclo[3.1.0]hexanes and their Stereospecific Reactions with Butyl-lithium

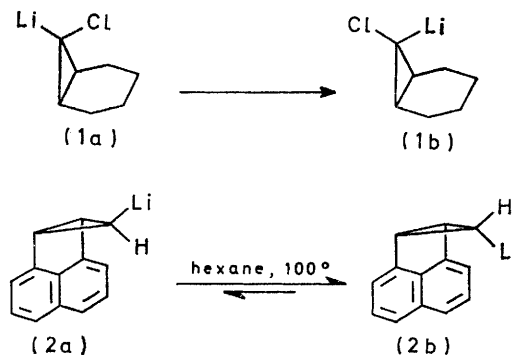
By H. Maskill, Department of Chemistry, University of Stirling, Stirling

6,6-Dibromo-3-oxabicyclo[3.1.0]hexane (8a) has been reduced by zinc-acetic acid, zinc-ethanolic potassium hydroxide, tributyltin hydride, and *n*-butyl-lithium followed by water to give mixtures of *exo*- and *endo*-6-bromo-3-oxabicyclo[3.1.0]hexanes (8d and e). The reaction of (8a) with tributyltin hydride is not stereoselective [(8d) : (8e) 48 : 52]. Reduction with zinc causes selective removal of the *endo*-bromine [(8d) : (8e) 62 : 38 with acetic acid and 3 : 1 with ethanolic potassium hydroxide]. Reduction with butyl-lithium followed by water is even more stereoselective [(8d) : (8e) *ca.* 9 : 1]. Both monobromides undergo stereospecific reactions with butyl-lithium followed by carbon dioxide (>99.5% retention of configuration). The n.m.r. spectra of the monobromides and carboxylic acids are reported and discussed.

SIMPLE cyclopropyl-lithium compounds are known to be configurationally stable^{1,2} and in this respect they resemble vinyl-lithium^{3,4} rather than alkyl-lithium^{3,5} derivatives. Calculations of the inversion energy barrier using the MINDO method gave a higher value for cyclopropyl carbanion (36.6 kcal mol⁻¹) than for vinyl carbanion (31.1 kcal mol⁻¹) and the latter figure is more than 7 kcal mol⁻¹ higher than values computed for simple alkyl carbanions.⁶

The known effect of groups such as cyanide, which have an electron-withdrawing mesomeric effect, bonded to a carbanionic cyclopropyl carbon is to reduce the energy barrier for inversion.^{2a,7} The α -chlorocyclopropyl-lithium (1a) has been reported⁸ to undergo partial isomerization to (1b) at -115 to -91° though the mechanism for this may not involve a unimolecular inversion. The aromatically substituted cyclopropyl-lithium compound (2a) has been reported⁹ to rearrange reversibly to (2b) in hexane solution at 100°. The authors suggested that some sort of favourable interaction between the lithium of (2b) and the aromatic system may be the driving force. This intramolecular

effect is completely suppressed with the more basic tetrahydrofuran (THF) as solvent. The effects of



intramolecular heteroatoms upon lithium-bearing cyclopropyl carbon atoms have not, until recently, been investigated.

⁴ (a) A. S. Dreiding and R. J. Pratt, *J. Amer. Chem. Soc.*, 1954, **76**, 1902; (b) F. G. Bordwell and P. S. Landis, *J. Amer. Chem. Soc.*, 1957, **79**, 1593; D. Y. Curtin and E. E. Harris, *ibid.*, 1951, **73**, 2716, 4519; D. Y. Curtin and J. W. Crump, *ibid.*, 1958, **80**, 1922; A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, 1957, **1**, 158.

⁵ R. L. Letsinger, *J. Amer. Chem. Soc.*, 1950, **72**, 4842; *Angew. Chem.*, 1958, **70**, 151.

⁶ M. J. S. Dewar and M. Shanshal, *J. Amer. Chem. Soc.*, 1969, **91**, 3654.

⁷ H. M. Walborsky and F. M. Hornyak, *J. Amer. Chem. Soc.*, 1955, **77**, 6026; 1956, **78**, 872.

⁸ G. Köbrich and W. Goyert, *Tetrahedron*, 1968, **24**, 4327.

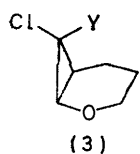
⁹ G. Wittig, V. Rautenstrauch, and F. Wingler, *Tetrahedron*, 1966, **22**, Suppl. 7, 189.

¹ D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, 1961, **83**, 862; M. J. S. Dewar and J. M. Harris, *ibid.*, 1969, **91**, 3652.

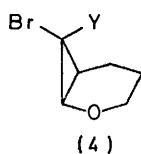
² (a) H. M. Walborsky, *Records Chem. Progr.*, 1962, **23**, 75; H. M. Walborsky and M. P. Periasamy, *J. Amer. Chem. Soc.*, 1974, **96**, 3711; (b) H. M. Walborsky and F. J. Impastato, *J. Amer. Chem. Soc.*, 1959, **81**, 5835; H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, 1964, **86**, 3283.

³ D. Y. Curtin and W. J. Koehl, jun., *J. Amer. Chem. Soc.*, 1962, **84**, 1967.

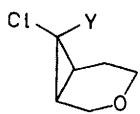
The oxygen atoms in (4a)—(7a) cause only the *endo*-halogens to undergo lithium-halogen exchange with methyl- or butyl-lithium.¹⁰ Compound (3a) in ether



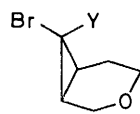
(3)
a; Y = Cl
b; Y = Li



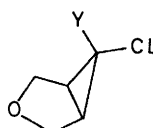
(4)
a; Y = Br
b; Y = Li



(5)
a; Y = Cl
b; Y = Li
c; Y = H



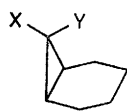
(6)
a; Y = Br
b; Y = Li
c; Y = H



(7)
a; Y = Cl
b; Y = Li
c; Y = H

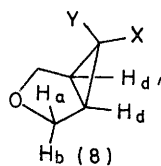
also undergoes only *endo*-lithiation, but in THF *endo*- and *exo*-lithiation occur in the ratio 1.6 : 1.

Besides controlling the stereoselectivity of the exchange reactions, the oxygen also stabilizes the carbenoids (3b)—(7b) with respect to α -elimination. Intramolecular co-ordination of the *endo*-lithium by the transannular oxygen was reported as the cause of this stabilization. However, it may be partly due to the electron-withdrawing inductive effect of oxygen, *i.e.* perhaps a corollary of an observation reported by Baird *et al.*¹¹ and corroborated in our work. The dibromo-compound (8a) is considerably more stable with respect



(1)

a; X = Li, Y = Cl
b; X = Cl, Y = Li
c; X = Y = Cl
d; X = Y = Br
e; X = Br, Y = Li
f; X = Li, Y = Br
g; X = Br, Y = CO₂H



a; X = Y = Br
b; X = Br, Y = Li
c; X = Li, Y = Br
d; X = Br, Y = H_{c'}
e; X = H_c, Y = Br
f; X = Li, Y = H_{c'}
g; X = H_c, Y = Li
h; X = CO₂H, Y = H_{c'}
i; X = H_c, Y = CO₂H
j; X = H_c, Y = H_{c'}

to cyclopropyl-allyl rearrangement than its carbocyclic analogue 6,6-dibromobicyclo[3.1.0]hexane,¹² and such a process involves a cationic intermediate. The oxygen of (8a), therefore, which destabilizes an electron-

deficient intermediate, may be expected to stabilize a corresponding anionic species.

The reaction of 7,7-dichlorobicyclo[4.1.0]heptane (1c) with butyl-lithium in THF-ether-light petroleum at -115° was reported by Köbrich and Goyert⁸ to favour *exo*- over *endo*-lithiation by a factor of 3—4. But the carbenoid with the lithium *exo*, *i.e.* the major product (1a), is considerably less stable than (1b) and undergoes partial isomerization to (1b) even below -100° . In contrast, it has been reported that the reaction of 7,7-dibromobicyclo[4.1.0]heptane (1d) in THF with butyl-lithium even at -140° followed by carboxylation gives only (1g) *via* (1e).¹³

Seyferth and Lambert¹⁴ have more recently reported that (1d) gives (1e) exclusively with butyl-lithium if, after mixing the reactants at -107° in THF, the temperature is raised to *ca.* -93° and a slight excess of the dibromide over butyl-lithium is used. If either the temperature is maintained at -124° or if butyl-lithium is in excess, both (1e) and (1f) are formed but always with the former predominating. Clearly, no intramolecular electronic effect may be invoked to account for the *opposite* stereoselectivities of the reactions of (1c) and (1d) with butyl-lithium, or for the higher stabilities of (1b) over (1a), and (1e) over (1f).

The present report is of the preparation of (8d and e) by methods including the lithium-bromine exchange of (8a) with butyl-lithium followed by protonation, and the stereospecific exchange reactions of (8d and e) with butyl-lithium. The role of the oxygen atom upon the selective reduction of (8a) and upon the configurational stability of the cyclopropyl-lithium compounds is discussed and the n.m.r. spectra of the new cyclopropyl bromides and cyclopropanecarboxylic acids are analysed.

Previous workers have commonly investigated the configurational stabilities of organo-lithium compounds by using enantiomeric halides and measuring the optical purity of the product after the organometallic compound has been quenched with an acid. There are difficulties in this procedure which give rise to inaccuracy especially if it is difficult to remove completely the optically active starting material from the product.^{2b} Also, the driving force for the configurational inversion is due only to the increase in entropy of racemization. By using compounds whose inversion of configuration would involve diastereoisomerization, we not only increase the thermodynamic driving force for the inversion process (in one direction), but also facilitate the analysis as g.l.c. may be used which gives a low limit of detection and, we believe, a high degree of accuracy.

The present cyclopropyl-lithium compounds are drawn as monomeric species with simple, covalent

¹⁰ K. G. Taylor, W. E. Hobbs, and M. Saquet, *J. Org. Chem.*, 1971, **36**, 369; K. G. Taylor and W. E. Hobbs, *Tetrahedron Letters*, 1968, 1221; see also K. G. Taylor and J. Chaney, *J. Amer. Chem. Soc.*, 1972, **94**, 8924; K. G. Taylor, W. E. Hobbs, M. S. Clark, and J. Chaney, *J. Org. Chem.*, 1972, **37**, 2436.

¹¹ M. S. Baird, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc. (C)*, 1969, 1173.

¹² J. Sonnenberg and S. Winstein, *J. Org. Chem.*, 1962, **27**, 748; L. Gatlin, R. E. Glick, and P. S. Skell, *Tetrahedron*, 1965, **21**, 1315.

¹³ T. Ando, K. Wakabayashi, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Japan*, 1972, **45**, 1576.

¹⁴ D. Seyferth and R. L. Lambert, jun., *J. Organometallic Chem.*, 1973, **55**, C53.

bonds¹⁵ even though alkyl-lithium compounds are known to be oligomeric in solution¹⁶ and the bonding, consequently, is not simple.^{16a,17} However, in the absence of precise knowledge of the molecular structures of these compounds in mixed solvents, monomeric structures have the advantage of ease of representation if not of accuracy.

RESULTS AND DISCUSSION

The cycloaddition of 2,5-dihydrofuran with dibromocarbene¹⁸ generated from bromoform and potassium t-butoxide, was described earlier¹⁹ as a low yield reaction and gives <6% (8a). The yield has been improved significantly by using the easier phase-transfer catalysis (p.t.c.) method.²⁰ Tetraethylammonium bromide, trimethyl(tetradecyl)ammonium bromide, and benzyltriethylammonium chloride were among the catalysts which were found to be effective. 2-Dibromomethyl-2,5-dihydrofuran¹⁹ is also produced with (8a) in the ratio *ca.* 35 : 65 at 0° and *ca.* 60 : 40 at room temperature. Our work-up procedure left (8a) as the single product which was isolated either by distillation at reduced pressure or, more effectively for small amounts, by preparative g.l.c.

The cycloaddition of 2,5-dihydrofuran with dibromocarbene generated by thermolysis of tribromomethyl(phenyl)mercury²¹ was attempted but gave a poor yield (<1%).

Reduction of Compound (8a).—A variety of methods is available for the selective reduction of *gem*-dihalogenocyclopropanes to halogenocyclopropanes.^{8,10,22} Reaction of (8a) with tributyltin hydride²³ was expected to be selective in favour of the *endo*-bromide (8e). Two monobromides which are separable by preparative g.l.c. were obtained in the ratio 48 : 52 however, and it was established that this ratio did not vary during the course of the reduction. One product is a crystalline solid, m.p. 60.5–61.5°, and the other a liquid at room temperature, m.p. 15.5–16.0°. The structures were assigned by n.m.r. spectroscopy (*vide infra*). Stereo-

selectivity in favour of the *exo*-bromide (8d) was anticipated¹⁰ and obtained by reaction of (8a) with butyllithium followed by an aqueous quench. The stereoselectivity, (8d) : (8e) *ca.* 9 : 1, is not significantly affected by modest variations in temperature or solvent.

TABLE I

Ratio of isomers formed by dehalogenation

Reactant	Method	Ratio of <i>exo</i> : <i>endo</i> monohalides	Ref.
(8a)	Zn-AcOH	64 : 36	a
(8a)	Zn-EtOH-KOH	3 : 1	a
(8a)	i, C ₄ H ₉ Li; ii, H ₂ O	9 : 1	a
(8a)	H ₂ Sn(C ₄ H ₉) ₃	48 : 52	a
(1c)	i, C ₄ H ₉ Li; ii, MeOH	1 : 3.9—9.1 : 1	b
(1d)	Zn-AcOH	1 : 5.7	24, a
(1d)	Zn-EtOH-KOH	1 : 2.9	25

^a This work. The ratio was affected by the experimental conditions, ref. 8.

Reduction of (8a) with zinc-acetic acid²⁴ gives (8d and e) in the ratio 64 : 36 at room temperature. It was shown that the ratio (8d) : (8e) was constant throughout the reduction and consequently that (8e) is not the major initial product which selectively suffers further debromination.

With zinc-ethanolic potassium hydroxide the same two products are obtained in the ratio 3 : 1 in a slower reaction at 80°. Reduction of (1d) with zinc gives *endo*- and *exo*-7-bromobicyclo[4.1.0]heptanes in the ratios 2.9 : 1 under basic conditions²⁵ and 5.7 : 1 under acidic conditions.^{24a} For other analogous *gem*-dibromocyclopropanes,^{24b} the selectivity of the zinc-acetic acid reduction method is even more greatly in favour of the formation of the *endo*(*cis*)-monobromide.

We ascribe this reversal of selectivity not to any serious difference in the steric requirements in replacing a methylene by an ether linkage, but to the ability of the oxygen in (8a) to direct the zinc preferentially *endo*. There are good analogies for a comparable effect when a neighbouring oxygen function is able to dominate the

²² A. J. Fry and R. H. Moore, *J. Org. Chem.*, 1968, **33**, 1283; C. W. Jefford, D. Kirkpatrick, and F. Delay, *J. Amer. Chem. Soc.*, 1972, **94**, 8905; H. Yamanaka, T. Yagi, K. Teramura, and T. Ando, *Chem. Comm.*, 1971, 380; H. Nozaki, T. Aratani, and R. Noyori, *Tetrahedron*, 1967, **23**, 3645; C. L. Osborn, T. C. Shields, B. A. Shoulders, C. G. Cardenas, and P. D. Gardner, *Chem. and Ind.*, 1965, 766; D. Seyferth and B. Prokai, *J. Org. Chem.*, 1966, **31**, 1702; R. Barlet and Y. Vo-Quang, *Bull. Soc. chim. France*, 1969, 3729.

²³ (a) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, 1963, **28**, 703; (b) T. Ando, H. Yamanaka, and W. Funasaka, *Tetrahedron Letters*, 1967, 2587; T. Ando, H. Yamanaka, F. Namigata, and W. Funasaka, *J. Org. Chem.*, 1970, **35**, 33; T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Amer. Chem. Soc.*, 1967, **89**, 5719; T. Ando, H. Hosaka, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Japan*, 1969, **42**, 2013; (c) H. G. Kuivila, *Accounts Chem. Res.*, 1968, **1**, 299.

²⁴ (a) R. E. Erickson, R. Annino, M. D. Scanlon, and G. Zon, *J. Amer. Chem. Soc.*, 1969, **91**, 1767; (b) C. L. Osborn, T. C. Shields, B. A. Shoulders, J. F. Krause, H. V. Cortez, and P. D. Gardner, *J. Amer. Chem. Soc.*, 1965, **87**, 3158; (c) K. Hofmann, S. F. Orochena, S. M. Sax, and G. A. Jeffrey, *J. Amer. Chem. Soc.*, 1959, **81**, 992; J. E. Hodgkins, J. D. Woodyard, and D. L. Stephenson, *ibid.*, 1964, **86**, 4080; R. Annino, R. E. Erickson, J. Michalovic and, B. McKay, *ibid.*, 1966, **88**, 4424.

²⁵ H. Yamanaka, R. Oshima, and K. Teramura, *J. Org. Chem.*, 1972, **37**, 1734.

¹⁵ G. Köbrich, *Angew. Chem. Internat. Edn.*, 1967, **6**, 41; 1972, **11**, 473.

¹⁶ (a) T. L. Brown, *Adv. Organometallic Chem.*, 1965, **3**, 365; *Pure Appl. Chem.*, 1970, **23**, 447; (b) H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, 1970, **92**, 4664; P. West and R. Waack, *ibid.*, 1967, **89**, 4395; L. M. Seitz and T. L. Brown, *ibid.*, 1966, **88**, 2174; D. Margerison and J. D. Pout, *Trans. Faraday Soc.*, 1971, **67**, 353.

¹⁷ H. F. Ebel, *Tetrahedron*, 1965, **21**, 699; R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Comm.*, 1969, 117; L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *J. Amer. Chem. Soc.*, 1969, **91**, 1057; F. J. Kronzer and V. R. Sandel, *Chem. and Ind.*, 1972, 210.

¹⁸ W. E. Parham and E. E. Schweizer, *Org. Reactions*, 1963, **13**, 55.

¹⁹ J. C. Anderson and C. B. Reese, *Chem. and Ind.*, 1963, 575; J. C. Anderson, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc.*, 1964, 4874.

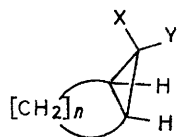
²⁰ L. Skattebol, G. A. Abskharoun, and T. Greibrokk, *Tetrahedron Letters*, 1973, 1367; E. V. Dehmow and J. Schönfeld, *Annalen*, 1971, **744**, 42; M. Makosza and M. Fedorynski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1971, **19**, 105 (*Chem. Abs.*, 1971, **75**, 19,745); F. Nerdel, P. Hentschel, W. Brodowski, and J. Brudrus, *Annalen*, 1971, **746**, 6.

²¹ D. Seyferth and J. M. Burlitch, *J. Organometallic Chem.*, 1965, **4**, 127.

stereoselectivity in cyclopropanations of oxygenated olefins by organometallic reagents.²⁶

N.m.r. Spectra of (8a, d, and e).—The n.m.r. spectrum of (8a) in CCl₄ has already been reported¹⁹ and comprises multiplets at τ 6.09 (4H) and 7.47 (2H). In benzene solution at 90 MHz, the chemical shift difference between *exo*- and *endo*-2- and -4-H is enhanced and the two doublets of an AB quartet are observed at τ 6.37 (2H) and 6.62 (2H, J_{AB} 9.3 Hz). The low field doublet is not split further by any other coupling and is ascribed to the *endo*-2- and -4-H which give dihedral angles of *ca.* 90° with 1- and 5-H respectively if the molecule is boat-like.^{10,27a} Boat-like structures have already been established for derivatives of bicyclo[3.1.0]hexane,²⁸ 3-oxa-6-azabicyclo[3.1.0]hexane,²⁹ and 6-azabicyclo[3.1.0]hexane³⁰ by X-ray crystallography, and recent microwave investigations³¹ of 3-oxabicyclo[3.1.0]hexane and bicyclo[3.1.0]hexane conclude that these too have such structures. The high field doublet of the AB quartet due to the *exo*-2- and -4-H is split further by unequal couplings (J *ca.* 2 Hz) with 1- and 5-H. These assignments are in accord with results from n.m.r. studies of thujane derivatives^{32,33} and other simpler bicyclo[3.1.0]hexane compounds.³⁴

The n.m.r. spectrum of the low melting monobromide was recorded at 90 MHz and spin-decoupling allowed



(9a) X = H, Y = Cl, $n = 4$
(9b) X = H, Y = Br, $n = 4$
(10a) X = Cl, Y = H, $n = 4$
(10b) X = Br, Y = H, $n = 4$
(10c) X = Br, Y = H, $n = 6$

determination of some of the coupling constants, as shown, and consequently the assignment of structure (8d). The most important difference between this spectrum and that of the crystalline monobromide is in the magnitudes of the coupling constants between 1- (and 5-) and 6-H. The smaller value of J 2.5 Hz corresponds to *trans*-vicinal coupling in the *exo*-monobromide (8d) and the larger J of 7.0 Hz corresponds to *cis*-vicinal coupling in the *endo*-monobromide (8e).^{10,23a,27}

The chemical shifts for *endo*-7-H in (9a and b) are very similar to each other (τ 7.44 and 7.42 respectively) but are at higher field by *ca.* 0.6 p.p.m. than the chemical shifts for the non-bridgehead cyclopropyl hydrogens in (10a–c) which in turn are very similar to each other (τ 6.86, 6.81, and 6.86 respectively).^{23a} Thus, these chemical shifts are not sensitive to small changes in the ring size or to the nature of the halogen but they are

²⁶ S. Winstein, J. Sonnenberg, and L. de Vries, *J. Amer. Chem. Soc.*, 1959, **81**, 6523; W. G. Dauben and G. H. Berezin, *ibid.*, 1963, **85**, 468; C. D. Poulter, E. C. Friedrich, and S. Winstein, *ibid.*, 1969, **91**, 6892.

²⁷ (a) S. Sternhell, *Quart. Rev.*, 1969, **23**, 236; (b) J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, 1962, **84**, 2249; H. M. Hutton and T. Schaefer, *Canad. J. Chem.*, 1962, **40**, 875.

²⁸ M. F. Grostic, D. J. Duchamp, and C. G. Chidester, *J. Org. Chem.*, 1971, **36**, 2929.

²⁹ L. M. Trefonas and T. Sato, *J. Heterocyclic Chem.*, 1966, **3**, 404.

³⁰ H. M. Zacharis and L. M. Trefonas, *J. Heterocyclic Chem.*, 1968, **5**, 343.

characteristically dependent upon configuration. It is seen that the 3-oxa-group in (8d and e) has a slight enhancing effect upon this chemical shift–configuration dependence.

The n.m.r. spectrum of the *endo*-monobromide (8e) has the high field component of the AB quartet due to 2- and 4-H₂ as a sharp doublet and the low field doublet is split further by coupling to the cyclopropane protons. This is the opposite order from that found for (8a), (8d), and other analogous¹⁰ compounds. Assuming that the well established geometrical dependence of coupling^{10,27a,34} applies in (8e), it must be *endo*-2- and -4-H which have the higher field chemical shift.

The n.m.r. spectrum of 3-oxabicyclo[3.1.0]hexane (8j) in CCl₄ shows an AB system due to 2- and 4-H₂ with doublets at τ 6.46 and 6.59.³⁵ The authors of ref. 35 did not assign the two components to *exo*- or *endo*-H but this is now possible. The high field doublet shows extra coupling to the cyclopropane protons and consequently must be assigned to *exo*-H.^{10,27a,34}

Comparison of the n.m.r. results of (8a, d, e, and j) in Table 2 shows that the single *endo*-6-Br of (8e) deshields

TABLE 2

N.m.r. results for (8)

Compound	H _a	H _b	H _c	H _{c'}	H _d	Solvent
(8j)	6.46	6.59	9.4–9.8 ^e		8.60	CCl ₄
(8d) *	6.07 ^a	6.40 ^a		7.42 ^b	8.03 ^c	CCl ₄
(8e) †	6.21 ^a	6.05 ^a	6.68 ^d		8.01 ^c	CCl ₄
(8a)		6.09 ^c			7.47	CCl ₄
(8h) ‡	6.07 ^a	6.27 ^a		8.40 ^b	7.78 ^c	CDCl ₃
(8i) §	5.82 ^a	6.18 ^a	8.19 ^{e,f}		8.02 ^{e,f}	CDCl ₃

* J_{ab} 8.8; $J_{ac'} = J_{ad} = J_{bc'} = 0$; $J_{c'd}$ 2.5; $J_{bd} \neq J_{bd'} \sim 1$ Hz.

† J_{ab} 8.5; $J_{ac} = J_{ad} = 0$; J_{bc} 0.6; $J_{bd} \neq J_{bd'} \sim 2$; J_{cd} 7.0 Hz.

‡ J_{ab} 8.8; $J_{ac'} = J_{ad} = J_{bc'} = 0$; $J_{bd} \sim 1$ Hz; $J_{c'd}$ 3.2 Hz.

§ J_{ab} 8.6; $J_{ac} = J_{ad} = J_{bc} = 0$; $J_{bd} \sim 1$; J_{cd} 8.0 Hz.^f

^a AB quartet. ^b Triplet. ^c Multiplet. ^d Triplet of triplets.

^e Complex doublet. ^f Obtained by analysis of the AB₃ system after irradiation at τ 6.18.

the *exo*-2- and -4-H by 0.54 p.p.m.; the deshielding effect upon the corresponding *endo*-H is smaller, 0.25 p.p.m. The *exo*-6-Br of (8d) has the larger deshielding effect, 0.39 p.p.m., upon *endo*-2- and -4-H and a smaller effect, 0.19 p.p.m., upon the corresponding *exo*-H. Taylor and his colleagues¹⁰ also reported that the chemical shifts of 2-H₂ of 3-oxabicyclic cyclopropanes (5a, c), (6a, c), and (7a, c) are systematically dependent upon the configuration of the substituent(s) at the non-bridgehead cyclopropane carbon.

The effects of 6-Br upon the chemical shifts of 1- and 5-H of the 3-oxabicyclo[3.1.0]hexane system are cumu-

³¹ T. B. Malloy, jun., *J. Mol. Spectroscopy*, 1974, **49**, 432; R. L. Cook and T. B. Malloy, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 1703; see also R. C. Lord and T. B. Malloy, jun., *J. Mol. Spec.*, 1973, **46**, 358; R. A. Creswell and J. W. Lafferty, *ibid.*, p. 371.

³² A. Dieffenbacher and W. von Philipsborn, *Helv. Chim. Acta*, 1966, **49**, 897.

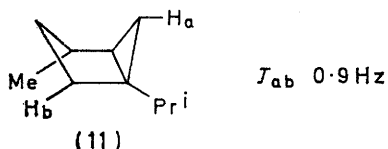
³³ H. E. Smith, J. C. D. Brand, E. H. Massey, and L. J. Durham, *J. Org. Chem.*, 1966, **31**, 690.

³⁴ P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, 1965, **30**, 771; S. Winstein, E. C. Friederich, R. Baker, and Y.-i. Lin, *Tetrahedron*, 1966, Suppl. 8, II, 621.

³⁵ T. Shono, A. Oku, T. Morikawa, M. Kimura, and R. Oda, *Bull. Chem. Soc. Japan*, 1965, **38**, 940.

lative and not significantly dependent upon configuration.

Finally, the n.m.r. spectrum of the crystalline monobromide showed a small but unambiguous long range coupling (J 0.6 Hz) between 6-H and the proton which causes the low field component of the AB quartet. Such coupling usually requires an approximately coplanar **W** arrangement of the four intervening bonds^{27a} and can only be between *exo*-2- (and -4-) and -6-H and confirms the crystalline product as (8e). The required geometrical relationship is particularly favourable if the molecule is boat-like. Comparable long range coupling (J 0.9 Hz) between H_a and H_b of (–)-*cis*-thujane (11) has already been reported³² and (11), like other bicyclo[3.1.0]hexane derivatives, is believed to be boat-like.



Carboxylation of (8f and g).—The reactions of (8d and e) with butyl-lithium were investigated using light petroleum (or pentane) and THF as solvents at several temperatures. In each case the resultant mixture was quenched either by the addition of an excess of solid carbon dioxide or by passing in an excess of gaseous carbon dioxide. Although carbon dioxide has been reported³⁶ to be an unsatisfactory electrophile for quenching some unsaturated organo-lithium compounds, it has several advantages for our purposes. It is believed to react with cyclopropyl-lithium compounds with retention of configuration at the nucleophilic centre;⁴ our results support this. Secondly, the acidic products and neutral reactants are easily separated for analysis. Thirdly, an excess of butyl-lithium in the reaction mixture can easily be confirmed by the detection of valeric acid among the products.

Although (8h), (8i), and valeric acid were not easily resolvable using common 2 m \times 1/8 in packed g.l.c. columns, the i.r. and n.m.r. spectra of the products showed that different acids were obtained from (8d and e). It was necessary to prove that the overall lithiation-carboxylation process had occurred with retention of configuration, and secondly to estimate the maximum amount of isomerization at the cyclopropyl-lithium stage which could have occurred.

It was easily shown that the purified acid obtained from the *exo*-bromide (8d) had the small vicinal coupling constant (J 3.2 Hz) between the different cyclopropyl protons and consequently that it was the *exo*-acid (8h).

The chemical shifts of the cyclopropyl protons of the acid from the *endo*-bromide (8e) are very similar in $CDCl_3$ and form a multiplet, τ 7.9–8.3. The AB quartet of 2- and 4- H_2 showed coupling between the bridgehead protons and the *exo*-2- and -4-H. By double

resonance of these *exo*-protons, an AB_2 pattern was observed for the cyclopropane protons and analysis³⁷ gave the parameters shown. The magnitude of the vicinal coupling between the different cyclopropyl protons (J 8.0 Hz) confirms the assigned structure (8i).²⁷

Comparison of the n.m.r. results for the two acids and two monobromides with those for the parent 3-oxabicyclo[3.1.0]hexane shows a significant difference in the substituents' effects. Unlike bromine, the carboxylic group causes substantial deshielding of *exo*- and *endo*-2- and -4-H regardless of the configuration at C-6. As carbon tetrachloride could not be used as solvent for the acids, a more quantitative comparison is not possible. A smaller configurational dependence of the deshielding effect of the 6-carboxy-group upon 6-H is also noted but there is a greater dependence upon configuration of deshielding of 1- and 5-H by carboxy than by bromine.

In order to establish the extent of the stereospecificity of the lithiation-carboxylation reactions, the crude acidic products had to be analysed, and this was not achieved by direct g.l.c. of the acids. The methyl esters of the acids were easily resolved on a 2 m \times 1/8 in 5% Apiezon L column as also were the trimethylsilyl esters. Although the methyl esters of valeric acid and (8h) could be made quantitatively from the acids *via* the sodium salts with methyl iodide in hexamethylphosphoramide by a recently described procedure,³⁸ the sodium salt of (8i) appeared to react more slowly. Consequently, as conversion of the free acids into the trimethylsilyl esters is rapid and quantitative,³⁹ this was preferred. It was possible to estimate <1% of any one in a mixture of the others.

The neutral fraction of unchanged bromide was easily analysed on any of several commonly used g.l.c. columns and in no case was isomerized bromide detected. The difference in retention times of (8d and e) (4.2 and 7.4 min respectively at 120°; 25 ml min⁻¹ on 5% Apiezon L) is remarkable for simple diastereoisomeric bromides.

The yields of carboxylic acids were never very high and were generally lower at the higher reaction temperatures. The experimental conditions were varied and it was confirmed that both (8f and g) could be formed from the respective bromides and that they react with carbon dioxide.

Compound (8d) gives the *exo*-acid (8h) under all conditions of solvent and temperature (up to 22°) which were tried but the initial lithiation in the absence of THF was slow as expected.^{5,15} After 10 min at 0° there was only a low conversion to (8f) and a high recovery of valeric acid and unchanged (8d). After 3 h at 0° before the addition of carbon dioxide, the monobromide completely reacted, but the recovery of acid was low (17%) with no trace (<0.3%) of product of inverted configuration. In the presence of THF, the reaction of (8d) with butyl-lithium is rapid at -77°.

³⁸ J. E. Shaw, D. C. Kuerth, and J. J. Sherry, *Tetrahedron Letters*, 1973, 689.

³⁹ C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, 1963, **85**, 2497.

³⁶ R. P. Dickinson and B. Iddon, *Tetrahedron Letters*, 1970, 975.
³⁷ R. J. Abraham, 'The Analysis of High Resolution N.M.R. Spectra,' Elsevier, Amsterdam, 1971, p. 55.

The reaction of the *endo*-bromide (8e) with butyllithium followed by the addition of carbon dioxide gave poorer yields of the acid. Only a very low recovery of acid was obtained using THF as solvent even when the organo-lithium compound was added to the excess of carbon dioxide as recommended by Dreiding and Pratt.^{4a} But in no case was a substantial recovery of the starting bromide obtained.

The conditions which were favourable for one were applied to the other but in no case tried was there any evidence to suggest that the acid formed was other than that of completely retained configuration (>99.5%). The 3-oxa-group therefore, although having an effect upon the yields of the reactions, does not facilitate inversion of configuration of the cyclopropyl-lithium compounds. These results are in remarkable contrast to the reaction of (2a) even though intramolecular co-ordination should be greater for (8g) than for (2b). It may be, however, that the inversion of configuration of (8f), though intrinsically more favourable than the corresponding reaction of (2a), is always less favourable than other intermolecular reactions. Organo-lithium compounds are known¹⁰ to react with methylene groups adjacent to an ether linkage and the cyclopropane group may have a further activating effect upon 2-H₂ of these compounds. Alternatively, intermolecular co-ordination between the oxygen of one organo-lithium with the lithium of another may be as effective as intramolecular co-ordination thereby removing the driving force for the inversion of (8f) to (8g).

EXPERIMENTAL

Analytical g.l.c. was done on Perkin-Elmer F11 and F30 chromatographs using 2 m × 1/8 in stainless steel packed columns and nitrogen as carrier (15 lb in⁻² on the F11 and 25 cm³ min⁻¹ on the F30): column A, 1.5% QF1 on AW-DMCS Chromosorb W; column B, 5% Apiezon L on AW-DMCS Chromosorb G; column C, 15% Carbowax 20M on Chromosorb W. Preparative g.l.c. was done on a Varian model 700 chromatograph using an 8 ft × 3/8 in aluminium column of 8% Apiezon L on Phase Prep A and nitrogen as carrier gas (150 cm³ min⁻¹). 90 and 60 MHz N.m.r. spectra were recorded on Perkin-Elmer R32 and R10 instruments at Stirling; 100 MHz spectra were recorded on a Varian HA100 instrument by P.C.M.U., Harwell.

6,6-Dibromo-3-oxabicyclo[3.1.0]hexane (8a).—To a mechanically stirred, ice-cold suspension of trimethyl(tetradecyl)ammonium bromide (1 g), 2,5-dihydrofuran (14.0 g, 0.2 mol), and bromoform (51.0 g, 0.2 mol) was added a solution of sodium hydroxide (45.0 g, 1.1 mol) in water (45 g) dropwise during 1 h. Vigorous stirring was continued for 6 h at 0°, then the reaction mixture was allowed to warm to room temperature overnight. The mixture was acidified with hydrochloric acid and extracted three times with ether. G.l.c. on column C (150°) showed (8a) and 2-dibromomethyl-2,5-dihydrofuran to be present in the ratio *ca.* 65:35. After evaporation of the dried, filtered ether solution, the residual brown oil was cautiously warmed under a reflux condenser with a solution of sodium hydroxide (10 g, 0.25 mol) in methanol (60 cm³) until an initial vigorous reaction had subsided, then at reflux

temperature for 4 h. Water was added and the mixture was extracted twice with ether. The combined ether phases were extracted twice with sodium hydrogen sulphite solution and once with brine, dried (MgSO₄), and filtered. After evaporation of the ether, the product (8.3 g, 17%) was isolated by fractional distillation at reduced pressure, b.p. 59–61° at 0.3 Torr. In other preparations, preparative g.l.c. (128°) was used to obtain smaller amounts of pure material, ν_{\max} (liquid film) 3060w, 2960, 2930, 2870, 1325, 1280, 1092, 1076, 1030, 900, 765, and 693 cm⁻¹. Details of the n.m.r. spectrum are given in the Discussion section.

Reduction of 6,6-Dibromo-3-oxabicyclo[3.1.0]hexane.—(a) Finely powdered zinc (0.6 g) was added in batches over *ca.* 15 min to a stirred solution of (8a) (0.515 g, 2.13 mmol) in acetic acid (3 cm³). After an initial increase in temperature, the mixture was stirred at room temperature for 16 h. Ether (20 cm³) was added and the solution was filtered. The filtrate was extracted with an excess of aqueous 2M-sodium hydroxide and the aqueous phase was re-extracted with more ether. Combined ether phases were extracted with brine, dried (MgSO₄), and filtered. The volume of the filtrate was reduced to *ca.* 1 cm³ by fractional distillation using a Hempel column. Pure (8d and e) were isolated by preparative g.l.c. (80°) in 21% (71 mg) and 36% (124 mg) yields respectively. [More careful fractionation of the products would have allowed the isolation of a higher yield of the more volatile *exo*-bromide (8d) as g.l.c. (column A; 100°) showed that the crude product mixture contained (8d):(8e) 62:38]. A sample of *endo*-6-bromo-3-oxabicyclo[3.1.0]hexane (8e) after preparative g.l.c. was triturated with pentane to leave crystals, m.p. 60.5–61.5°, ν_{\max} (KBr) 3050w, 2910, 2860, 1330, 1240, 1090, 1050, (8d):(8e) 62:38]. A sample of *endo*-6-bromo-3-oxa-1000, 955, 915, 890, 770, 743, and 600 cm⁻¹ (Found: *M*⁺, 161.9680. C₅H₇⁷⁹BrO requires *M*, 161.9681). Details of the n.m.r. spectrum are given in the Discussion section.

When a comparable reaction was monitored by g.l.c. (column C; 150°) after working-up portions after 3, 40, and 130 min, and 6.5 h, the ratio (8d):(8e) was constant as the concentration of (8a) decreased.

(b) Finely divided zinc (2 g, 31 mmol) was added to a stirred solution of (8a) (0.7 g, 2.9 mmol), potassium hydroxide (1 g, 19 mmol), and ethanol (10 cm³) at room temperature. Portions were removed and extracted between ether and dilute hydrochloric acid. The ether phase was analysed by g.l.c. (column C; 150°). The ratio (8d):(8e) (3:1) was unchanged after 3 and 90 min but the reaction was very slow. After 3.5 h at 80°, the ratio (8d):(8e) was still unchanged but the amount of dibromide was much reduced. After 12 h at 80° less than 1% dibromide remained and (8d):(8e) was still 3:1.

(c) A solution of (8a) (0.986 g, 4.07 mmol) and tributyltin hydride (1.669 g, 4.80 mmol) was stirred at room temperature. Portions were directly analysed by g.l.c. (column B; 145°) and the ratios of (8a, d, and e) were measured after 0.5, 1, 3, 3.25, and 4 h.

The ratio (8d):(8e) was constant at 48:52 throughout and the amount of dibromide dropped to *ca.* 5% after 4 h. A further amount of tributyltin hydride (0.518 g, 1.49 mmol) was added and the solution was subsequently monitored by g.l.c. and i.r. No dibromide (<0.05%) was detected after 16 h but an excess of reducing agent was still detectable after 3 days. Throughout, the ratio (8d):(8e) was constant. Fractional distillation at 5 Torr gave two

fractions: 78 mg (12%), (8d) : (8e) 66 : 34 and 75 mg (11%), (8d) : (8e) 40 : 60. A sample of (8d) was purified by preparative g.l.c., m.p. 15.5–16.0° (corr.), ν_{\max} (liquid film) 3050w, 2960, 2930, 2860, 1330, 1194, 1075, 1004, 891, and 836 cm^{-1} . Details of the n.m.r. spectrum are given in the Discussion section. The mass spectrum showed parent peaks at m/e 162 and 164, as expected for $\text{C}_5\text{H}_7^{79}\text{BrO}$ and $\text{C}_5\text{H}_7^{81}\text{BrO}$, and fragmentation consistent with the assigned structure.

(d) Butyl-lithium (14.3 cm^3 of a 2.1M-solution in hexane, 30 mmol) was added to a stirred solution of (8a) (6.6 g, 27.3 mmol) in absolute THF (50 cm^3) at -77° under argon during ca. 20 min. After 49 min, water (20 cm^3) was added and the mixture was allowed to warm to room temperature. The mixture was extracted between pentane and water and the pentane phase was dried and filtered; (8d and e) were present in the ratio 89 : 11. Fractional distillation at atmospheric pressure removed most of the pentane and (8d) (2.47 g, 68%) was isolated by distillation (b.p. 73–75° at 34 Torr). When the lithiation was done at 0 rather than -77° , and with a slight deficiency of butyl-lithium, the reduction was incomplete but the ratio (8d) : (8e) was effectively unchanged (87 : 13).

Carboxylations of Compounds (8d and e).—The following features were common to all the reactions. Butyl-lithium (Alfa) was used as a solution in hexane and was delivered from a special burette in which the solution was kept under argon. The solution was stable at room temperature and was standardized by titration. The volumes of this solution and number of mmoles of butyl-lithium used are quoted. All reactions were done in scrupulously dry apparatus under argon with stirring. Light petroleum and pentane were fractionally distilled from P_2O_5 and THF was fractionally distilled from potassium. The work-up involved extraction between water (or dilute sodium hydroxide) and ether. The ether solutions were dried (MgSO_4) and analysed by g.l.c. (column B; 120°) directly. The aqueous phases were acidified with concentrated hydrochloric acid and extracted with ether. These ether solutions of acidic products were dried (Na_2SO_4), filtered, and evaporated. Samples of the residual acids (5–10 mg) were transferred to small vials fitted with synthetic rubber septa. Tri-sil (Pierce Chemical Company; 100–300 μl) was injected through each septum and the vial was shaken vigorously for 1 min. The resultant solution was analysed by g.l.c. (column B; 125°).

exo-6-Bromo-3-oxabicyclo[3.1.0]hexane (8d).—(a) Butyl-lithium in hexane (2.2 cm^3 , 4.62 mmol) was added to a stirred solution of (8d) (0.73 g, 4.48 mmol) in dry pentane (5 cm^3) and dry THF (5 cm^3) at -75° . Further THF (8 cm^3) was added in an unsuccessful attempt to dissolve the white suspension which formed. After 5 min at -75° , an excess of crushed, solid carbon dioxide was added and the mixture was allowed to warm to room temperature. After work-up, no unchanged bromide was detected in the neutral fraction and the acid fraction gave a sticky solid (0.33 g, 58%). By a combination of trituration and recrystallization, a pure sample of (8h) (139 mg, 24%) was obtained, m.p. (from ether) 145.5–146.5° (Found: C, 56.4; H, 6.15. Calc. for $\text{C}_6\text{H}_8\text{O}_3$: C, 56.25; H, 6.3%), ν_{\max} (KBr) 3300–2500br, 1700, 1430, 1280, 1225, 1180, 1160, 1060, 870, and 650 cm^{-1} . The retention time of the trimethylsilyl ester of this pure acid (column B; 125°; 25 $\text{cm}^3 \text{min}^{-1}$) was 13.4 min. [The retention times of the trimethylsilyl esters of pure *endo*-acid (*vide infra*) and

valeric acid under identical conditions were 11.9 and 2.6 min respectively. Co-injection of the authentic derivatives showed well-resolved, sharp peaks due to the trimethylsilyl esters of (8h and i).] By analysis of the residual acid after isolation of pure (8h) it was shown that the maximum amount of (8i) as a contaminant in the total yield of (8h) was <0.5%.

(b) The same procedure but stirring the reaction mixture at 0° for 35 min before the addition of carbon dioxide caused only a smaller recovery of crude acid (32%) and no increase in the maximum proportion of *endo*-contaminant (<0.4%).

(c) When the butyl-lithium addition was done at 22° and the stirring was continued for a further 1 h before the addition of solid carbon dioxide, the yield of crude *exo*-acid was only 14% and the maximum proportion of the *endo*-acid in this was <0.3%. No acidic product was obtained if the lithiated *exo*-bromide was heated to 80° before the addition of carbon dioxide.

(d) Butyl-lithium in hexane (0.5 cm^3 , 1.0 mmol) was added to a stirred solution of (8d) (71 mg, 0.436 mmol) in dry light petroleum (b.p. 40–60°; 5 cm^3) at -77° . The solution was warmed to 0° and stirred for 10 min before dry gaseous carbon dioxide was passed in for 40 min. After work-up a substantial amount of unchanged (8d) remained in the neutral fraction and the acidic product was largely valeric acid. The small amount of 3-oxabicyclo[3.1.0]hexane-6-carboxylic acid (ca. 2–3%) was more than ca. 95% (8h). A comparable reaction in which the lithiated compound was stirred in dry light petroleum for 3 h at 0° before addition of gaseous carbon dioxide still gave a low yield of (8h) (17%), but the *endo*-contaminant was accurately <0.3% and all the bromide had been consumed.

endo-6-Bromo-3-oxabicyclo[3.1.0]hexane (8e).—(a) Butyl-lithium in hexane (0.6 cm^3 , 1.3 mmol) was added to a stirred suspension of (8e) (0.129 g, 0.79 mmol) in dry THF (1 cm^3) and dry pentane (6 cm^3) at -30° . After 2 min an excess of solid carbon dioxide was added and stirring was continued until the mixture had warmed to room temperature. Only a trace of (8e) was detected in the neutral fraction and the acidic product (87 mg) contained valeric acid and (8i). The *endo*-acid was contaminated with <0.1% of the *exo*-isomer. Pure *endo*-acid (25 mg, 25%) was isolated by trituration, m.p. (from ether) 174–175° (Found: C, 56.55; H, 6.45%), ν_{\max} (KBr) 3500–2500br, 1690, 1422, 1330, 1250, 1081, 892, 822, and 572 cm^{-1} . See Discussion section for n.m.r. details. A sample of this acid was used to make the trimethylsilyl ester in order to show that it was resolvable from the trimethylsilyl ester of the *exo*-acid (*vide supra*).

(b) Butyl-lithium in hexane (0.5 cm^3 , 1.0 mmol) was added to a stirred solution of (8e) (164 mg, 1.0 mmol) in dry pentane (7 cm^3) at 0°. After 1 min, an excess of solid carbon dioxide was added and stirring was continued until the mixture had warmed to room temperature. After work-up, the neutral fraction was shown to contain some (8e). The crude acidic fraction (80 mg) was (8i) contaminated with valeric acid and <0.3% (8h). A pure sample of (8i) (20.5 mg, 16%) was isolated by trituration with pentane.

(c) Butyl-lithium in hexane (0.4 cm^3 , 0.84 mmol) was added to a stirred solution of (8e) (0.120 g, 0.73 mmol) in dry pentane (4 cm^3) and dry THF (4 cm^3) at -77° . After 10 min an excess of crushed, solid carbon dioxide was added and the mixture was allowed to warm to room temperature.

After work-up, the neutral fraction contained no (8e). The crude acid was (8i) (30 mg, 32%) contaminated with valeric acid and a pure sample was obtained by recrystallization from ether. This was used to take the n.m.r. spectrum (see Discussion section).

(d) Butyl-lithium in hexane solution (1.0 cm³, 2.1 mmol) was added to (8e) (0.126 g, 0.77 mmol) in dry THF (5 cm³) and dry light petroleum (b.p. 40–60°; 1 cm³) at –77°. After 15 min, dry, gaseous carbon dioxide was passed in for 1 h as the mixture warmed to room temperature. After work-up, only a trace of unchanged bromide was detected in the neutral phase and the acidic product (65 mg) was largely valeric acid. The small amount of *endo*-acid (8i) (*ca.* 6 mg, 5%) was shown to contain <0.5% *exo*-acid by analysis of the trimethylsilyl esters.

(e) Butyl-lithium in hexane solution (1.0 cm³, 2.1 mmol) was added to a solution of (8e) (0.116 g, 0.71 mmol) in dry

THF (7 cm³) at –77°. After 10 min, the contents of the flask were poured onto an excess of crushed, solid carbon dioxide. After the contents of the flask had warmed to room temperature overnight, the mixture was worked-up in the usual way. No (8e) was detected in the neutral fraction; the acidic product (39 mg) was largely valeric acid and the small amount of (8i) was contaminated with <0.5% of (8h).

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