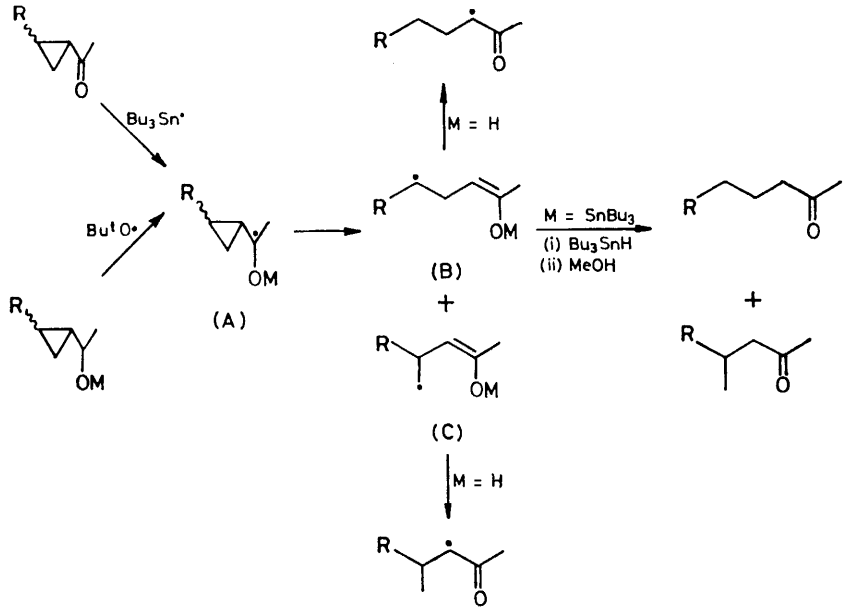
The Regioselective Ring-opening of Ring-substituted Cyclopropylcarbinyl Radicals: Variation of the Substituent

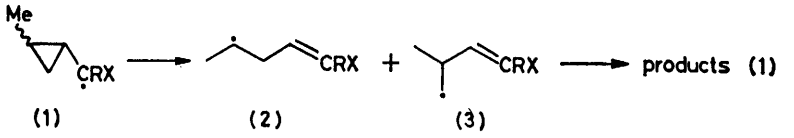
By **Marie Castaing, Michel Pereyre,*** and **Max Ratier,** Laboratoire de Chimie Organique et Laboratoire de Chimie des Composés Organiques du Silicium et de l'Étain associé au C.N.R.S., Université de Bordeaux 1, 351 cours de la Liberation, 33405 Talence, France
Peter M. Blum and **Alwyn G. Davies,*** Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ

The *cis*- and *trans*-2-ethyl- and 2-t-butyl-cyclopropylcarbinyl radicals (A; M = H or Bu_3Sn; R = Et or Bu^t) were generated by the addition of tributyltin radicals to the appropriate ketone, or abstraction of hydrogen from the appropriate carbinols, and the intermediate radicals and the ultimate products were monitored by e.s.r. spectroscopy



and by g.l.c. respectively. It is shown that the ethyl and t-butyl substituents exert the same directive effect as the methyl group in that whereas the *cis*-reactants undergo ring opening to give predominantly the secondary alkyl radicals (B) the *trans*-reactants give the thermodynamically less stable primary alkyl radicals (C).

In recent papers [1-8] we have reported experiments on the regioselectivity of the ring-opening of *cis*- and *trans*-2-methylcyclopropylcarbinyl radicals (1; R = H or alkyl, X = H, OH, or $OSnBu_3$).



The intermediate radicals were monitored by e.s.r. spectroscopy, or the ultimate products by g.l.c. Consistently, *cis*-(1) was found to undergo ring-opening to give mainly the secondary alkyl radical (2), but, remarkably, *trans*-(2) gives mainly the thermodynamically less stable *primary* alkyl radical (3).

As yet we have been able to make only tentative suggestions regarding the way in which this regioselectively is controlled by the electronic and steric effects of the constituent groups of the molecule. To provide a more secure basis for any interpretation which may evolve we have now studied the effect of varying the alkyl substituent in the ring, and we report here the results of experiments, by both techniques, on *cis*- and *trans*-2-ethyl-, 2-t-butyl-, and 2-phenyl-cyclopropyl compounds.

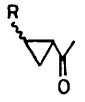
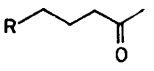
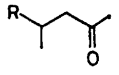
RESULTS

The *cis*- and *trans*-2-ethyl- and 2-t-butyl-cyclopropyl methyl ketones (4; R = Et or Bu^t) were treated with neat tributyltin hydride in the presence of azoisobutyronitrile (AIBN) at 80 °C. Under these conditions homolytic ring-opening is induced by the tributylstannyl radical [equation (2)]. The vinyloxytin compounds which were formed were decomposed with methanol and the resulting ketones (7) and (8) were analysed by g.l.c. Ring opening is complete under these conditions; it is only at relatively low temperature (*ca.* −20 °C) that the radical (5) is trapped by tributyltin hydride, and the carbinol corresponding to the

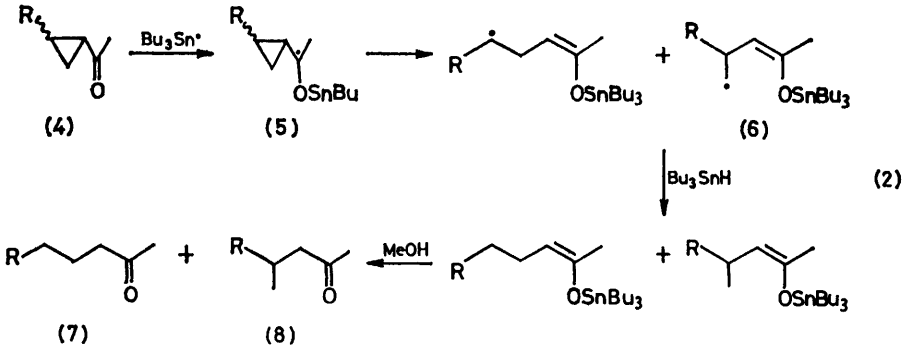
initial ketone can be detected. The results are collected in Table 1.

TABLE 1

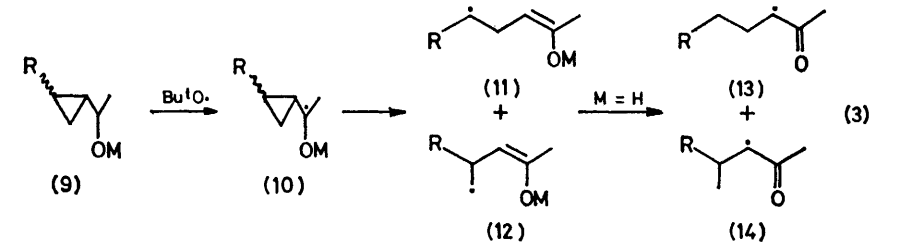
Products from the reduction of ring-substituted cyclopropyl methyl ketones with tributyltin hydride at 80 °C

R in	Product composition (%)		Overall yield of ketones (%)
			
trans-Me	25	75	85 [4]
cis-Me	90	10	65 [4]
trans-Et	31	69	80
cis-Et	92	8	88
trans-Bu^t	37	63	84
cis-Bu^t	100	0	100
trans-Ph	100	0	95 [3]
cis-Ph	100	0	93 [3]

The e.s.r. experiments were carried out by photolysing di-t-butyl peroxide in the presence of the cyclopropylcarbinol (9; M = H) in cyclopropane solvent in the cavity of an e.s.r. spectrometer.



The cyclopropylcarbinyl radicals (10) which are first formed undergo rapid ring-opening, and the spectra which are observed at low temperature are those of the but-3-enyl radicals (11) or (12). At higher temperature the radicals (11) and (12) undergo intramolecular 1,5-transfer of hydrogen from enolic oxygen to carbon,[9] and the spectra of the enoxyl radicals (13) and (14) are observed, providing a double check on the direction of ring-opening. Chirality at the carbinol carbon atom in (9) is lost when the radical (10) is formed, and, as would be expected, the *erythro*- and *threo*-isomers of the alcohols gave identical spectra.



The radicals *trans*-(9; R = Bu^t; M = Bu$_3$Sn) were also generated by photolysing hexabutylditin in the presence of the appropriate cyclopropyl methyl ketone, and the radicals (11) or (12) were monitored spectroscopically; unlike hydrogen, the Bu$_3$Sn group does not migrate from oxygen to carbon.

The radicals which were detected, and their e.s.r. spectra, are listed in Table 2. Reactions, which are not reported, were also carried out with the *cis*-substituted carbinols, but the signal-to-noise ratio of the spectra was not good enough to permit unambiguous interpretation.

DISCUSSION

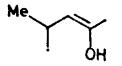
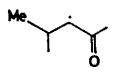
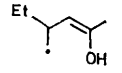
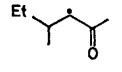
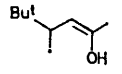
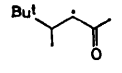
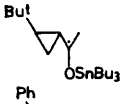
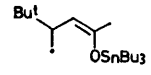
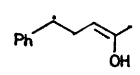
We have shown that when isobutyl *trans*-2-methylcyclopropyl ketone is reduced with tributyltin hydride of increasing concentration in benzene solution, the ratio of the acyclic ketones formed through the primary and secondary alkyl radicals respectively reaches a maximum constant value (*ca.* 80 : 20) at *ca.* 1.5M-Bu$_3$SnH, when kinetic control of the products is complete.[6] In the present experiments the concentration of tributyltin hydride is *ca.* 2.0M, and we conclude that the results reported in Table 1 are essentially those represented by kinetic control and that whereas the *cis*-2-ethyl and *cis*-2-t-butyl stannyloxyalkyl radicals (5) undergo ring opening to give predominantly secondary alkyl radicals, the corresponding *trans*-radicals give principally the primary alkyl radicals (6).

The but-3-enyl radicals (12) (Table 2) formed by the ring-opening reactions (3) show values of a(Hα) which are approximately constant at 22 G, but values of a(Hβ) which decrease from 31 to 22 G as the bulk of the substituent R increases in the sequence H < Me < Et < Bu^t. Similarly the enoxyl radicals (14) all show values of a(Hα) of *ca.* 19 G, but a(Hβ) decreases from 21 to 8 G in the same sequence. This presumably reflects the increasing tendency of these types of radicals to adopt the average conformations (15) and (16) as the bulk of the group R increases in the series Me, Et, and Bu^t, and this places the β-hydrogen close to the nodal plane of the p-orbital containing the unpaired electron.

Only the primary alkyl radicals (12) and their derived

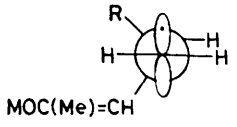
TABLE 2

E.s.r. spectra of radicals from the ring-opening of cyclopropylcarbinols in cyclopropane solution

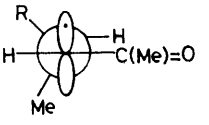
Cyclopropylcarbinyl radical	Radical observed	t/°C	a(Hα)/G	a(Hβ)/G
		−111	22.0(2)	31.3(2) [g]
		−34	18.9(1)	20.8(2) [g]
		−86	21.7(2)	27.8(1) [g]
		−9	18.8(1)	9.6(1) [g,c]
		−94	21.5(2)	26.5(1)
		−14	18.7(1)	7.6(1)
		−110	21.8(2)	21.8(1)
		+40	19.2(1)	7.5(1)
		−130	21.9(2)	29.9(1)
		−80		[d]

[a] From the mixed *erythro*-/*threo*-alcohols.[10] [b] From both the *erythro*- and *threo*-alcohols.[10] [c] The assignments of the hyperfine coupling constants were in error interchanged in ref. 9. [d] Broad unresolvable signal of a benzyl radical.

enoxyl radicals (14), as listed in Table 2, could be detected by e.s.r., and the concentration of any of the secondary alkyl radicals (11) and their derived enoxyl radicals (13) must be below the limits of detection



(15)



(16)

(*ca.* 10%) imposed by the noise level of the spectrometer. Again then, the effect of a *trans*-2-alkyl substituent in causing the ring-opening of the hydroxyalkyl radical (10; M = H) to give a primary rather than a secondary alkyl radical is not confined to the methyl group, but it extends also to the ethyl and t-butyl groups.

The greater proportion of secondary isomer in the preparative experiments may, of course, be associated with the higher reaction temperatures employed.

The effect of a phenyl substituent in the 2-position was also examined briefly by both techniques. Both the *cis*- and *trans*-substituted cyclopropylcarbinyl radicals now undergo ring-opening to give exclusively only the secondary radicals: any regioselectivity of the kind observed with alkyl substituents is clearly over-ridden by the effect of resonance stabilisation in the benzylic radical which is formed.

EXPERIMENTAL

Starting Materials.—*cis*- and *trans*-2-ethyl- and 2-t-butylcyclopropyl methyl ketones were obtained by chromic acid oxidation of the corresponding cyclopropylcarbinols which were prepared by means of Simmons–Smith propanation of the appropriate allylic alcohols. It should be noted that the carbinols can exist as *threo*- and *erythro*-isomers.[10] Full experimental details and characterisation of the products have been published elsewhere.[10]

Methyl *trans*-2-phenylcyclopropyl ketone was obtained by cyclopropanation of commercial *trans*-benzylideneacetone (Prolabo) by a published method.[11]

Methyl *cis*-2-phenylcyclopropyl ketone was prepared by catalytic semihydrogenation of 1-phenylbut-1-yn-3-ol to methyl-*cis*-styrylcarbinol,[12] which was then subjected to cyclopropanation [13] and oxidation with chromic acid.[14] The characteristics of the cyclopropyl compounds were in agreement with published data.[15]

Reduction of Cyclopropyl Ketones with Tributyltin Hydride.—Equimolecular amounts of the reagents (usually 1 mmol) and *ca.* 5 mol % of AIBN were sealed under argon in a small Pyrex tube, and heated in a bath at 80 °C for 15 h. The tube was then cooled and opened; a few drops of methanol were added and the products analysed by g.l.c. (20% Carbowax 20M on Chromosorb W 80—100, *t* 65—100 °C, helium). The products were identified by comparison with authentic samples which were prepared as follows.

Reference Compounds.—*Heptan-2-one.* This was a commercial sample (Fluka). *4-Methylhexan-2-one.* Ethylmagnesium bromide (0.15 mol) in ether was added slowly at room temperature to pent-3-en-2-one (0.10 mol) in the presence of a catalytic amount of cuprous iodide. The product was hydrolysed with a saturated solution of ammonium chloride to yield 4-methylhexan-2-one, b.p. 138—140 °C, δ(CCl_4) 0.82—1.02 (9 H, b, $CH_3CH_2CHCH_3$), 2.03 (3 H, s, CH_3), and 2.13—2.28 (2 H, b, CH_2).

6,6-Dimethylheptan-2-one. Methyl vinyl ketone (0.1 mol) was slowly added to an ethereal solution of neopentylmagnesium bromide (0.1 mol) containing a trace of cuprous iodide. The mixture was heated under reflux for a few hours and then worked up in the usual way to yield the ketone, b.p. 80—83 °C at 30 mmHg, δ(CCl_4) 0.88 [9 H, s, $C(CH_3)_3$], 0.9—1.75 (4 H, b, CH_2CH_2), 2.01 (3 H, s, CH_3), 2.18—2.40 (2 H, t, CH_2).

4,5,5-Trimethylhexan-2-one. Pivalaldehyde was condensed with acetone in the presence of sodium methoxide to give neopentylideneacetone (0.01 mol) [16] which was then treated with methylmagnesium iodide (0.02 mmol) in the presence of cuprous iodide. The reaction was incomplete, and the product showed signals of 4,5,5-trimethylhexan-2-one {δ(CCl_4) 0.86 [9 H, s, $C(CH_3)_3$] and 2.01 (3 H, s, CH_3)} as well as those of neopentylideneacetone {δ(CCl_4) 1.08 [9 H, s, $(CH_3)_3$], 2.12 (3 H, s, CH_3), and 5.65—6.72 (2 H, AB pattern, J_{AB} 15 Hz, olefinic protons)}.

To confirm these assignments, methyl *trans*-2-t-butylcyclopropyl ketone was reduced with tributyltin hydride on

a preparative scale. The n.m.r. spectrum of the product showed the presence of both 6,6-dimethylheptan-2-one (minor product) and 4,5,5-trimethylhexan-2-one (major product). Since the acyclic and cyclic ketones are easily separated by analytical g.l.c., the assignments of structure are unambiguous.

E.s.r. Technique.—Samples of the cyclopropyl reactant and the reagent for generating radicals (di-t-butyl peroxide or hexabutylditin) in cyclopropane were sealed *in vacuo* in Suprasil silica tubes, and photolysed in the cavity of a Varian E4 spectrometer fitted with a Philips S.P. 500 or Thorn 1000 W ME/D high-pressure mercury lamp and quartz lens system.

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