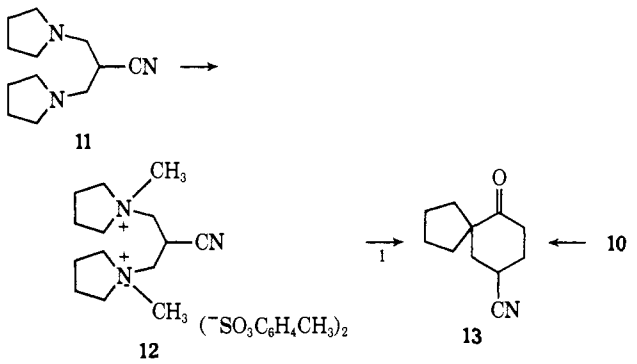
of the pyrrolidine ring which precludes the formation of the corresponding isomer. After hydrolysis of the iminum salt, the stable conformation of configuration **6** is undoubtedly assumed. Parallel observations of this kind of phenomena are seen in the synthesis of bridged bicyclic compounds.[3b]

The combination of the pyrrolidine enamine of acetylcyclopentane (**1**) and the nitrile corresponding to ester **2**, $\alpha$-(chloromethyl)acrylonitrile (**10**),[9] also provides the spiro framework **13** but the relative inaccessability of this particular alkylation–Michael reagent encouraged the development of a useful alternative. Cyanoacetic acid, pyrrolidine, and formaldehyde undergo facile bis-Mannich[10] condensation with concomitant decarboxylation to yield 1,3-bis(pyrrolidino)-2-cyanopropane (**11**) (40% yield, bp 120–122° (0.15 mm); $\nu_{max}^{CHCl_3}$ 2980, 2260 cm$^{-1}$; $\tau$ 7.12 (1 H, t), 7.16–7.60 (envelope), 8.03–8.42 (envelope)). Reaction of this diaminonitrile **11** with methyl *p*-toluenesulfonate in refluxing acetonitrile gives the bis quaternary salt **12** (highly hydroscopic) which can be utilized directly




in the annelation reaction. Condensation of **1** and **12** in acetonitrile produces **13** in 30% (mp 84–85°; bp 120–122° (0.25 mm); $\nu_{max}^{CHCl_3}$ 2940, 2245, 1704 cm$^{-1}$; $\tau^{CDCl_3}$ 6.9 (1 H, heptet), 7.3–8.6 (envelope of hydrogens with strong absorptions at 7.60, 7.85, and 8.35)).

The generality of these pathways to spiro compounds was further demonstrated by the conversion of acetylcyclohexane enamine to methyl spiro[5:5]undecan-1-one-4-carboxylate (homolog of **4**) (bp 95–100° (0.1 mm); $\nu_{max}^{CHCl_3}$ 1735, 1710, 1440, 1230 cm$^{-1}$; $\tau^{CDCl_3}$ 6.30 (3 H, s), 7.00–8.90 (envelope with strong peaks at 7.60, 7.80, and 8.50)).

The extensions of this reaction to other systems and the further use of these products in synthesis are continuing. The utilization of such spiro structures in the synthesis and study of angularly substituted decalins is described in the accompanying communication.

(9) R. P. Nelson, Ph.D. Dissertation, University of Michigan, 1967; A. F. Ferris and I. Marks, *J. Org. Chem.*, **19**, 1971 (1954).
(10) C. Mannich and E. Ganz, *Ber.*, **55**, 3486 (1922).
(11) Visiting Professor of Chemistry, 1970–1971; to whom inquiries should be addressed at: University of Wisconsin, Madison, Wis.

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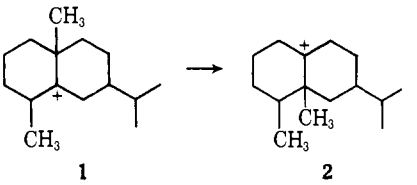
## Spiro Intermediates in Sesquiterpene Rearrangements and Synthesis

*Sir:*

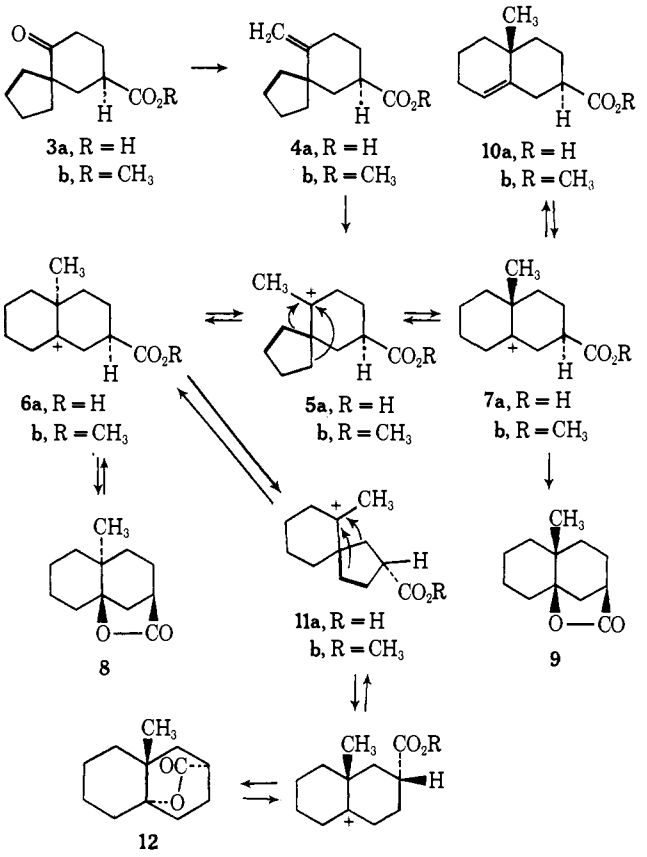
The eremophilane-type sesquiterpenes have long been considered to be derived from species of the eudesmane structure by migration of the angular methyl group (**1** → **2**).[1] Similar migrations have been proposed to occur in a variety of sesquiterpene and steroid systems[2] as well as in a model series.[3a] Nevertheless, Erdtman and Norin[4] have noted that it is surprising that the angular methyl of structures such as nootkatene

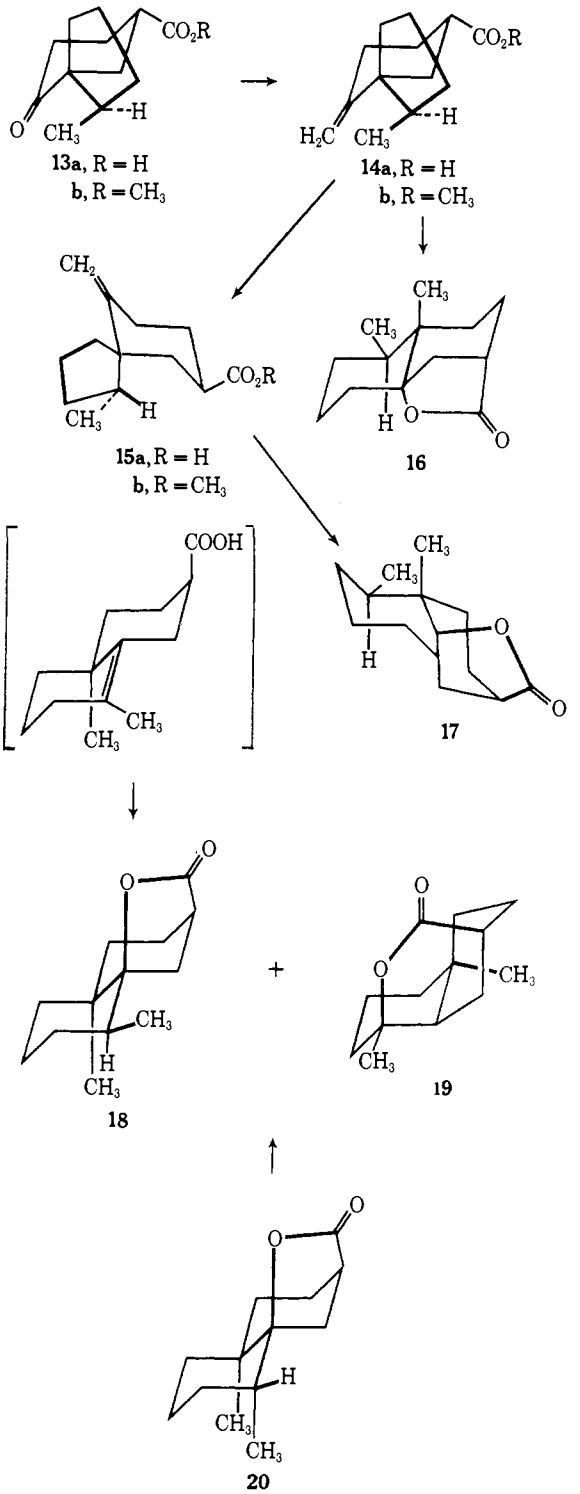



and nootkatone which would be expected on the basis of these biosynthetic hypotheses to have the same $\alpha$ orientation as the isopropyl group, in fact, has the wrong, $\beta$, orientation. In the course of synthetic studies to sesquiterpenes *via* spiro intermediates, we have made an observation relating to the mechanistic chemistry of these types of structures which suggests an alternative pathway to methyl migration.

A convenient synthetic route to angularly substituted decalins develops from a one-step synthesis of spiro keto ester **3b**.[5] Treatment of the corresponding acid **3a** with methylene triphenylphosphorane in dimethyl sulfoxide[6] produced the spiromethylene acid **4a**[7] (85% yield; mp 40–43°; $\nu^{CHCl_2}$ 2980, 1715, 1648 cm$^{-1}$; $\tau^{CDCl_3}$ 0.40 (1 H, s), 5.25 (2 H, broad s), 7.00–8.55 (envelope with sharp peaks at 7.75 and 8.40)). Treatment of **4a** with boron trifluoride in acetic acid[8] at room temperature effected rearrangement (quantitative) to a 1:1 mixture of two $\gamma$-lactones **8** (previously prepared;[3a] mp 70.2–70.8°; $\nu^{CHCl_3}$ 1780, 1460, 1240 cm$^{-1}$; $\tau^{CDCl_3}$ 8.95 (3 H, s)) and **9** (mp 87–88°; $\nu^{CHCl_3}$ 1772, 1300, 1115 cm$^{-1}$; $\tau^{CDCl_3}$ 8.98 (3 H, s)). Rearrangement of the spiro ester **4b** under the same conditions gave only the single configurational isomer **10b** ($\nu^{CHCH_3}$ 2950, 1735, 1660 cm$^{-1}$; $\tau^{CDCl_3}$ 4.55 (1 H, 6s), 7.30–8.60 (envelope), 8.92 (3 H, s)) previously prepared by Heathcock[3b] and used as an intermediate

(1) R. Robinson, "The Structural Relations of Natural Products," Clarendon, Oxford, 1955, p 12.
(2) See, for example: (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959; (b) P. deMayo, "Molecular Rearrangements," Part II, P. deMayo, Ed., Interscience, New York, N. Y., 1964; and (c) P. deMayo, "The Higher Terpenoids," Interscience, New York, N. Y., 1959.
(3) (a) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, 24, 3753 (1968); (b) *ibid.*, 24, 1801 (1968); (c) C. H. Heathcock and Y. Amons, *ibid.*, 24, 4917 (1968). We thank Dr. Heathcock for his help in providing comparison spectral data.
(4) H. Erdtman and T. Norin, *Fortschr. Chem. Org. Naturst.*, 24, 245 (1966).
(5) D. J. Dunham and R. G. Lawton, *J. Amer. Chem. Soc.*, 93, 2073 (1971).
(6) E. J. Corey and M. Chaykovsky, *ibid.*, 84, 866 (1962); 87, 1345 (1965).
(7) Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.
(8) See J. W. Rowe, A. Malera, D. Arigoni, O. Jeger, and L. Ruzicka in "Festschrift Prof. Dr. Arthur Stoll," Birkhaeuser, Basel, 1957, p 886, for the introduction of the concept at this route. Also, see *Helv. Chim. Acta*, **40**, 1 (1957).




in the synthesis of eudesmol sesquiterpenes.[3b] γ-Lactones **8** and **9** are kinetic products formed by the unexpected equal migration of both spiro bonds followed by capture of each resulting decalin cation (**6a**, **7a**) by the carboxyl function. In the case of the ester **4b**, trapping of the cation does not occur. The equilibrium allows the unstable trans ester methyl decalin cation **6b** to return to the spiro framework **5b** with subsequent rearrangement of the alternate spiro bond yielding, after proton elimination, the more thermodynamically stable cis ester methyl structure **10b**.

Studies by Heathcock on angular methyl migration in this framework were accomplished with acid **10a**.[3] Refluxing formic acid converted **10a** to a 2:1 equilibrium of γ-lactone **8** and a δ-lactone **12**. The pathway was reasonably pictured as carboxyl group epimerization and cation formation followed by γ-lactone capture as well as methyl migration and δ-lactone capture. Nevertheless the formic acid epimerization did not seem a likely step and a sequence (**10** → **5** → **6** → **8**) related to the chemistry suggested by our study appeared most plausible. Indeed, when acid **10** with deuterium in α position was treated with excess refluxing formic acid, both γ- and δ-lactones (**8** and **12**) produced had the same deuterium content as their precursor. Thus, epimerization of the carboxyl must take place through ring contraction to a spiro system rather than by epimerization. There is the further implication that δ-lactone does not arise from methyl migration but instead from contraction of the ring bearing the carboxyl function followed by migration of the alternate bond of this new spiro system **11** to give, after capture, the δ-lactone product.

In a similar fashion spiro keto acid **13a** (mp 125–126°; $\nu$ 3100, 2970, 1710, cm$^{-1}$; $\tau^{CDCl_3}$ 8.95 (3 H, 6d), 6.70–8.70 (envelope)) was converted to the methylene acid **14a** (oil; $\nu^{CDCl_3}$ 2990, 1708, 1640, 1445, 1200 cm$^{-1}$; $\tau^{CDCl_3}$ −1.64 (1 H, s), 5.15 (1 H, 6s), 5.34 (1 H, 5s), 6.35 (1 H, m) 7.00–8.70 (envelope), 9.02 (3 H, d)). Ester formation by diazomethane treatment followed by methoxide methanol epimerization afforded only isomer **15b** ($\nu$ 1730, 1640, 1430, 1165, 1125 cm$^{-1}$; $\tau$ −0.35 (1 H, s), 5.15 (1 H, 6s), 5.35 (H, 6s), 6.32 (H,s) 7.00–8.70 (envelope), 9.32 (3 H, d)) which was hydrolyzed to the acid **15a** ($\nu^{CDCl_3}$ 2990, 1708, 1640, 1445 cm$^{-1}$; $\tau$ −0.35 (1 H, s), 5.15 (1 H, s), 5.35 (1 H, s), 9.35 (3 H, d)). Room temperature formic acid treatment of **14a** yielded a γ-lactone assigned structure **16**

(liquid, $\nu$ 1780, 1480, 1180, 1080 cm$^{-1}$; $\tau^{CCl_4}$ 9.05 (3 H, s), 9.25 (3 H, d)) while the epimeric acid **15a** yielded $\gamma$-lactone **17** (mp 99.5–100.5°; $\nu$ 1780, 1460, 1125 cm$^{-1}$; $\tau$ 9.10 (3 H, s), 9.18 (3 H, d)). In both examples, migration of the methine carbon prevails over methylene migration[9] even when this latter group has a high axial preference. More vigorous treatment of $\gamma$-lactone **16** with refluxing formic acid resulted in the recovery of only starting material and a trace of as yet unidentified $\delta$-lactone. Further formic acid treatment of $\gamma$-lactone **17** produced quantitatively the same equilibrium mixture of $\gamma$-lactone **18** and $\delta$-lactone **19** obtained by Heathcock[3c] from lactone **20**. Besides defining the rearrangement this route provides a simple and efficient synthetic entry to the eudesmane-type sesquiterpenes.

These pathways involving two discrete spiro intermediates may be involved in the interconversion of eudesmane and certain eremophilane sesquiterpenes.[10] Such a sequence not only leads to the correct relative and absolute configurational relationships but also provides a further link between the recognized associations in sesquiterpene chemistry (eudesmol → hinesol).[11] Appropriate $^{14}C$ labeling studies in this model system and on synthetic eudesmol (*in vivo*) are anticipated.

(9) The sequence parallels the situation with spirodienone rearrangements. See ref 2b, p 1028.

(10) The mechanistic sequence **7** → **5** → **6** → **11** → **12** is illustrative. Replacing the 6-$CO_2R$ function with an isopropyl group and attaching a 4-methyl group demonstrates the natural product interrelationships. In the model system all compounds are enantiomeric mixtures and only one enantiomer is shown.

(11) See N. H. Anderson, M. S. Falcone, and D. D. Syidal, *Tetrahedron Lett.*, 1759 (1970); D. F. MacSweeney, R. Ramage, and A. Sattar, *ibid.*, 557 (1970).

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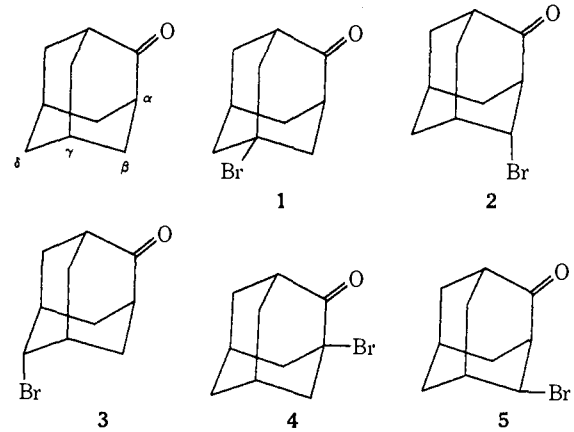
## Substituent Effect of the Carbonyl Group on Free-Radical Substitution. Bromination of Adamantanone

*Sir:*

Despite a number of studies concerning the free-radical substitution of adamantanes,[1] the nature of the effects of 1 substituents is not, at present, fully understood.[2] The effect of 2 substituents of adamantanes on the reactivity problem, on the other hand, has never been investigated.

Now we wish to report the free-radical bromination of adamantanone, the first study of the free-radical substitution of polycyclic ketones as well as of 2-substituted adamantanes. Considerable deactivation of the hydrogens $\alpha$ to the carbonyl is an important conclusion of the present study. Stereoselective equatorial substitution on the $C_\beta$ radical is another interesting point. Spectra of isomeric monobromoadamantanones are also described.

Five initial products, separated by means of preparative glpc (silicone SE 30 and poly(ethylene glycol) column), of the reaction of adamantanone and a brominating reagent (bromotrichloromethane, *N*-bromosuccinimide (NBS), or dibromomethane) in the presence of di-*tert*-butyl peroxide under nitrogen at 100–110° were determined to be isomeric monobromoadamantanones (**1**, **2**, **3**, **4**, and **5**, in the order of glpc elution from a poly(ethylene glycol) column). Melting points and spectra of the five bromo ketones are shown in Table I.




A high-frequency shift in $\nu_{C=O}$ and a small hypsochromic shift in $\lambda_{max}$ of **4**, which has not been reported in the literature,[3] are in good agreement with the reported ir and uv spectra of $\alpha$(e)-bromocyclohexanone derivatives.[5]

Favorskii rearrangement was also useful for distinguishing between isomeric bromo ketones. On treatment with alkaline solution (potassium hydroxide in aqueous ethanol) only **2** and **4** were converted, as expected, to known bicyclo[3.3.1]non-2-ene-7-carboxylic acid[4] and 1-noradamantanecarboxylic acid,[6] respectively.

In Table II are summarized the relative amounts of the five products, which were ascertained to correspond to the kinetically controlled product distribution.[7]

As shown in Table II, the reaction took place preferentially at the $C_\gamma$ position. An important observation was that the other bridgehead position, $C_\alpha$, $\alpha$ to the carbonyl, had considerably reduced reactivity

(1) (a) P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, 90, 4122 (1968); (b) G. J. Gleicher, J. L. Jackson, P. H. Owens, and J. D. Unruh, *Tetrahedron Lett.*, 833 (1969); (c) I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *ibid.*, 4069 (1969).

(2) It has been reported that the relative rates of the bridgehead hydrogen abstraction from 1-substituted adamantanes by trichloromethyl[1a] or atomic bromine[1b] were correlated with use of the Taft equation. The bridgehead-to-bridge product ratio, a measure of the effect of 1 substituents on the bridge positions, can be correlated with $\sigma^*$ when the trichloromethyl is an abstracting species. On the contrary, no such correlation is possible in the case of bromine as an attacking species. In chlorocarbonylation, the bridgehead-to-bridge product ratio may best be understood on steric grounds.[1c]

(3) All other monobromoadamantanones were reported elsewhere: **1**, Table I, footnotes *d* and *i*; **3**, Table I, footnote *i*; **5**, Table I, footnote *g*; **2**, Table I, footnotes *f* and *g* and ref 4.

(4) A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968).

(5) (a) R. C. Cookson, *J. Chem. Soc.*, 282 (1954); (b) N. J. Leonard and F. H. Owens, *J. Amer. Chem. Soc.*, 80, 6039 (1958).

(6) B. R. Vogt and R. E. Hoover, *Tetrahedron Lett.*, 2841 (1967).

(7) The reverse reaction of the intermediate radicals with hydrogen bromide[8] was negligible, for the product ratio showed no appreciable change in the course of the reaction. The authors also found that hydrogen bromide had little effect on the bridgehead-to-bridge product ratio of the free-radical bromination of adamantane.[9]

(8) D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *J. Amer. Chem. Soc.*, 91, 7398 (1969), and references therein.

(9) I. Tabushi, S. Kojo, Y. Aoyama, and Z. Yoshida, unpublished results.