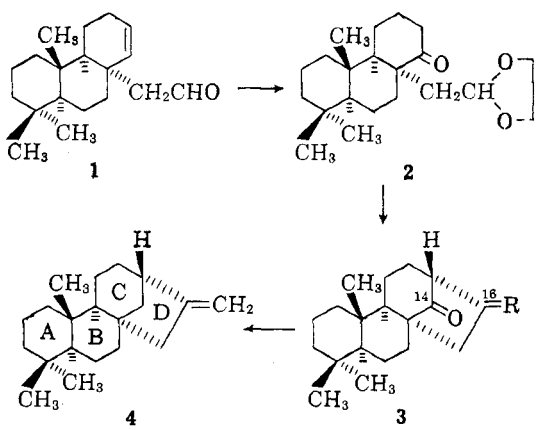
Communications TO THE EDITOR

The Total Synthesis of *dl*-Kaurene[1]

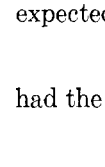
Sir:

We recently reported the synthesis of *dl*-8β-carbomethoxy-13-podocarpanone,[2,3] a key intermediate in the total synthesis of phyllocladene,[4] from the aldehyde (**1**) by oxidation and recyclization of the resulting tricarboxylic acid. This process served to convert the 8α-substituted B/C-*cis* ring fusion of the aldehyde (**1**) to the *trans* fusion required by the natural diterpene. Of more general utility would be a method whereby an aldehyde such as 1 could be cyclized to the desired bicycloöctane ring system directly such that there was functionality available on each bridge. Depending on the type of bicyclic system constructed, this method could serve in the synthesis of such di-



terpenoid natural products as steviol,[5] cafestol,[6] garryfoline,[7] and kaurene.[8] We report such a method here and, in particular, its use in the total synthesis of *dl*-kaurene (**4**).

Hydroboration[9] of the ethylene acetal (b.p. 130–135° (0.02 mm.); C, 78.94; H, 10.57) of the aldehyde (**1**) led to a mixture of 13- and 14-hydroxy acetals which on oxidation with Jones reagent[10] and chromatography on Florisil could be separated into the 14-keto acetal (**2**) (26%; m.p. 84.5–85.5°; C, 75.37; H, 10.15) and its 13-keto isomer (42%; m.p. 139–141°; C, 75.54; H, 10.26). In order to determine which of the two ketones obtained was the 14-keto acetal (**2**), the ketone obtained in lower yield (suspected to be the 14-ketone due to the hindrance to attack by boron at the 14-position) was reduced with lithium–ammonia, the acetal hydrolyzed in aqueous acid and the resulting hemiacetal oxidized with Jones reagent.[10] In this fashion, a γ-lactone (m.p. 78–79.5°; C, 78.54; H, 10.56; $\nu_{max}^{HCCl_3}$ 1780 cm.$^{-1}$) was obtained, thus confirming that the oxygen was in the 14-position.

When the acetal was removed from the ketone (**2**) itself by brief warming in aqueous mineral acid, the product was an hydroxy ketone (96%; m.p. 135–136°; C, 78.68; H, 10.48) rather than the expected keto aldehyde. That this hydroxy ketone had the bridged structure (3, R = ) was shown by oxidation with Jones reagent[10] to the dione (**3**, R = O) (90%; m.p. 196–197°; C, 79.17; H, 9.83), the infrared spectrum of which revealed the presence of a five-membered ring ketone ($\nu_{max}^{HCCl_3}$ 1765 cm.$^{-1}$) as well as a six-membered ring carbonyl ($\nu_{max}^{HCCl_3}$ 1730 cm.$^{-1}$). Molecular models of this dione show that the 14-ketone is considerably more hindered than the 16-ketone, and it was not surprising to find that, even in the presence of excess methylenephosphorane,[11] *dl*-14-ketokaurene (3, R = CH_2) (m.p. 108–109°; C, 84.10; H, 10.60) was obtained in 81% yield. The final stage of the synthesis was then effected by employing the Barton forcing conditions[12] of the Wolff–Kishner reduction whereby *dl*-kaurene (**4**) (m.p. 44–47°; C, 87.90; H, 11.97) was obtained in 65% yield. The infrared spectrum of the synthetic hydrocarbon (**4**) was identical with that of an authentic sample of

(1) Grateful acknowledgment is due the National Institutes of Health who made this work possible through a research grant (RG-9067).

(2) R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, No. **17**, 1 (1960); see also R. B. Turner and P. E. Shaw, *ibid.*, No. **18**, 24 (1960).

(3) Steroid numbering is used throughout, and although formulas for only one enantiomer are drawn, they are taken to represent a racemate except where indicated.

(4) R. B. Turner and K. H. Gänshirt *Tetrahedron Letters*, 231 (1961).

(5) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

(6) C. Djerassi, M. Cais, and L. A. Mitscher, *ibid.*, **81**, 2386 (1959).

(7) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Fegdor, and J. Herran, *ibid.*, **77**, 4801, 6633 (1955).

(8) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *Tetrahedron Letters*, No. **24**, 18 (1960).

(9) H. C. Brown, K. L. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960).

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(11) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954).

(12) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(−)-kaurene,[13] thus confirming the identity of the synthetic and natural products.

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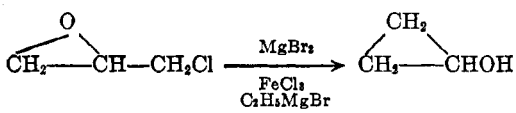
(13) The authors are indebted to Professor L. H. Briggs for making this specimen available through the auspices of Dr. S. Rutledge.

A One-Step Synthesis of 1-Substituted Cyclopropanols

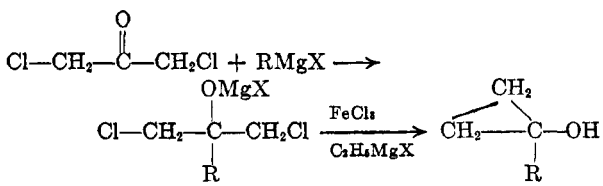
Sir:

We recently showed that a variety of cyclopropanols may be prepared by suitable modifications of standard synthetic procedures.[1] Cottle[2] had originally prepared cyclopropanol by the action of a Grignard reagent on a mixture of epichlorohydrin, magnesium bromide, and ferric chloride. This method may be extended to the synthesis of substituted cyclopropanols,[1,3] but yields are low and



the products are difficult to purify. In addition, it is usually tedious to prepare the requisite epoxide. A consideration of probable mechanism for the reaction led us to the following one-step synthesis of 1-substituted cyclopropanols.

Commercial 1,3-dichloroacetone (1 equiv.) in ether was added to an ethereal solution of phenylmagnesium bromide. After the addition was complete an ethereal solution of ethylmagnesium bromide (3 equiv.) and a solution of ferric chloride (0.10 equiv.) in ether were added simultaneously over a period of 1 hr. A very pronounced evolu-



tion of gas ensued. The reaction mixture was hydrolyzed with an ice-cold ammonium chloride solution and worked up in the usual way. After removal of the ether and cooling, the 1-phenylcyclopropanol crystallized. The yield was 48%. In the synthesis of a variety of other 1-substituted cyclopropanols by this process yields have approximated 50% after crystallization or distillation. This sequence will, we believe, make cyclopropanols extremely attractive starting materials for a variety of synthesis.

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(1) C. H. DePuy, L. R. Mahoney, and K. L. Eilers, *J. Org. Chem.*, **26**, 3616 (1961).

(2) (a) J. K. Magrane and D. L. Cottle, *J. Am. Chem. Soc.*, **64**, 484 (1942); (b) C. W. Stahl and D. L. Cottle, *ibid.*, **65**, 1782 (1943).

(3) G. M. Dappen, Ph.D. thesis, Iowa State University, 1961.

A New and Convenient Synthesis of Acyl Isocyanates

Sir:

We wish to report a new and convenient synthesis of acyl isocyanates (I) which involves the reaction of primary amides with oxalyl chloride.

A suspension of the amide in ethylene dichloride is treated with a slight excess of oxalyl chloride, and the mixture is heated under reflux for 4–16 hr. The solvent is removed and the acyl isocyanate is isolated by direct distillation *in vacuo*. Moisture must be rigorously excluded. The acyl isocyanates which we have prepared by this method are shown in Table I.

TABLE I
ACYL ISOCYANATES (I)

			Reported[1b]		
R	Yield, %	B.p., °C. (mm.)	B.p., °C. (mm.)	Yield, %	ν_{NCO} (cm.$^{-1}$) liquid
$ClCH_2$—	64	50–55 (20)	..	..	2250
Cl_2CH—	68	135 (35)	..	..	2250
Cl_3C—	60	80–85 (20)	..	..	2250
$C_6H_5CH_2$—	36	85 (3)	118 (20)	40	2250
	97	105.5 (1.6)	..	..	2275
C_6H_5—	75	97–98 (23)	90 (20)	50	2225
$(C_6H_5)_2CH$—	37	136–140 (1–1.2)	..	..	2225

This method appears far superior in convenience, yield, and scope (α-halogen compounds) to the only other reported[1] method for the preparation of acyl isocyanates—the reaction of an acid chloride with silver cyanate. Although the preparation of alkyl or aryl isocyanates by the reaction of amines with phosgene is well known, this method is not applicable to the preparation of acyl isocyanates since the reaction of phosgene with primary amides leads to nitriles[2] or complex mixtures.

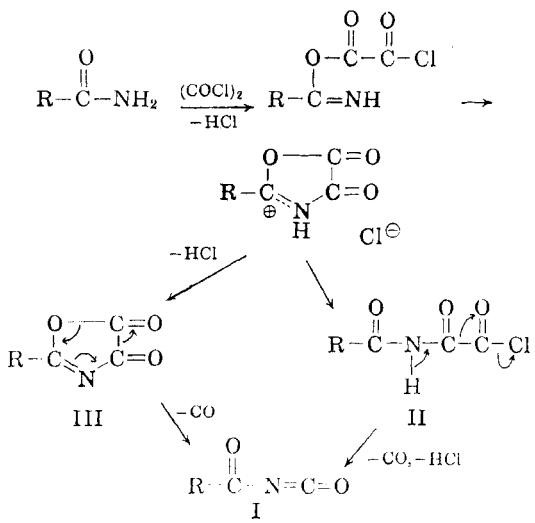
(1) (a) O. C. Billeter, *Ber.*, **36**, 3213 (1903); (b) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1595 (1940).

(2) R. Greenhalgh (to Imperial Chemical Industries, Ltd.), Brit. Patent 488,036 (June 29, 1938).

The acyl isocyanates, which we have prepared, exhibit typically strong —N=C=O absorption at 2225 to 2275 cm.$^{-1}$. Hoyer[3] has reported that the characteristic absorption of acetyl isocyanate occurs at 2246 cm.$^{-1}$ (CCl_4). The acyl isocyanates are very rapidly hydrolyzed on treatment with water. Acyl ureas, carbamates, and thiocarbamates are formed on reaction with amines, alcohols, and mercaptans.

Diacyl ureas were isolated in small yield in some cases as side products in the preparations. These must have been formed by reaction of the isocyanate with the starting amide. The formation of diacyl ureas by the reaction of oxalyl chloride with primary amides has been reported by Bornwater[4] and Stoughton[5] who caused two moles of the amide to react with one mole of oxalyl chloride.

We envision the formation of the acyl isocyanates as proceeding *via* acyl oxamic acid chlorides (II) or cyclic intermediates (III).



The intermediacy of II or III (or both) and the evidence for O-acylation *vs.* N-acylation of the amide will be discussed in forthcoming publications.

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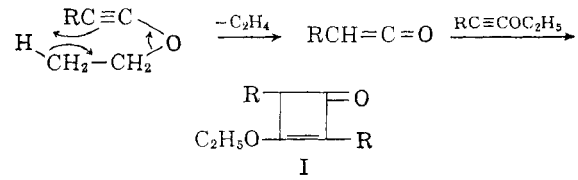
(3) H. Hoyer, *Ber.*, **89**, 2677 (1956).
(4) M. J. Bornwater, *Rec. trav. chim.*, **31**, 118 (1912).
(5) R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

Cycloaddition of Dimethylketene and Ethoxyacetylene

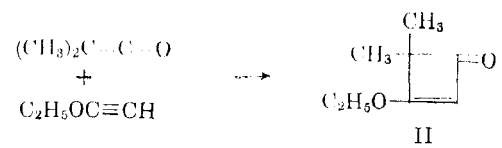
Sir:

The cycloaddition of ketenes to alkoxyacetylenes was first suggested by Nieuwenhuis and Arens[1] who found that pyrolysis of ethoxyacetylenes[2] gave ethoxycyclobutenones (I). This reaction apparently involves a concerted elimination of an aldoketene from the ethoxyacetylene, followed by cycloaddition of the ketene and acetylenic ether.



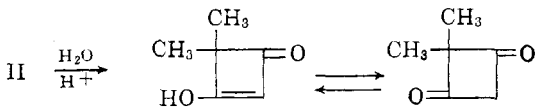
The ready addition of diphenylketene to ethoxyacetylene and 1-methoxy-1-propyne supported this mechanism, although the actual formation of alkoxycyclobutenones was obscured by the formation of rearrangement products[3,4] and by another mode of cycloaddition involving a benzene nucleus of the diphenylketene.[5,6] A recent publication has provided unequivocal evidence for formation of the alkoxycyclobutenone from diphenylketene and ethoxyacetylene.[7]

Although dimethylketene apparently is less reactive than diphenylketene in thermal cycloaddition reactions,[8] we found that dimethylketene and ethoxyacetylene combined in acetonitrile to give an 80% yield of 3-ethoxy-4,4-dimethyl-2-cyclobuten-1-one (II), b.p. 62–63° (2.5 mm.), $n^{20}D$ 1.4583; infrared maxima at 5.69 and 6.35 μ.[9] *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.6; H, 8.5. The n.m.r. spectrum[10] of II, taken on the pure liquid, showed peaks at the following positions: single at −192 c.p.s. (C=CH); quartet at −169 c.p.s. and triplet at −156 c.p.s. (—OCH_2CH_3); singlet at −46 c.p.s. [C-$(CH_3)_2$].



(1) J. Nieuwenhuis and J. F. Arens, *Rec. trav. chim.*, **77**, 761 (1958).
(2) J. Ficini, *Bull. soc. chim. France*, 1367 (1954).
(3) J. Nieuwenhuis and J. F. Arens, *Rec. trav. chim.*, **77**, 1153 (1958).
(4) J. F. Arens in "Advances in Organic Chemistry: Methods and Results," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, ed., Interscience Publishers, Inc., New York. N. Y., 1960, p. 193.
(5) E. F. Jenny, K. Schenker, and R. B. Woodward, *Angew. Chem.*, **73**, 756 (1961).
(6) D. H. R. Barton, J. N. Gardner, R. C. Petterson, and O. A. Stamm, *Proc. Chem. Soc.*, 21 (1962).
(7) J. Druey, E. F. Jenny, K. Schenker, and R. B. Woodward, *Helv. Chim. Acta*, **45**, 600 (1962).
(8) J. D. Roberts and C. M. Sharts, "Organic Reactions," Vol. 12, J. Wiley and Sons, Inc., New York, N. Y., 1962, p. 27.
(9) Infrared spectra were determined on a Perkin-Elmer 421 instrument with a dual grating interchange.
(10) All n.m.r. spectra were determined on a Varian Model V4300B instrument at 40 Mc. Peak positions are reported in cycles per second relative to tetramethylsilane as an internal standard.

Unlike the diphenylketene adduct, which isomerizes on gentle heating to a 1-naphthol, II is stable at temperature up to 150°. Hydrolysis in 5% hydrochloric acid solution at room temperature gave a 76% yield of 3-hydroxy-4,4-dimethyl-2-cyclobuten-1-one (III), m.p. 131–132°. *Anal.* Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.1; H, 7.0. The infrared spectrum (KBr pellet) showed two broad bands centered at 4.22 and 5.31 μ, a sharp band at 5.88 μ, and broad multiple bands at 6.6 to 7.5 μ. The n.m.r. spectrum of a 20% solution in dimethylformamide showed single peaks at -492 c.p.s. (—OH), -182 c.p.s. (C=CH), and -49 c.p.s. [$C(CH_3)_2$].



III IV

III is the enolic form of the mixed dimer of ketene and dimethylketene, the first known cyclobutanedione-type dimer (IV) involving ketene.[11] It is a relatively strong acid (pK_a 2.6) like the isomeric solid dimer of methylketene[12] (pK_a 3.0).[13]

Spectral data indicated that III remained in the enol form in such solvents as dimethylformamide, dimethylsulfoxide, pyridine, and acetone, but in chloroform solution the compound existed as the cyclic diketone IV. In the latter case, the infrared spectrum showed no absorption at 4.22, 5.31, 5.88, and 6.6–7.5 μ; a sharp band appeared at 5.70 μ. The n.m.r. spectrum of the chloroform solution showed only single peaks at -155 c.p.s. (CH_2) and -57 c.p.s. [$C(CH_3)_2$]. It is interesting that the acidic dimer of methylketene did not show this behavior, but remained in the enol form in chloroform solution.

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(11) During the preparation of this Communication, H. H. Wasserman reported the synthesis of II and III at the 141st Meeting of the American Chemical Society, Washington, D. C., March 28, 1962. II was prepared from ethoxyacetylene, isobutyryl chloride, and triethylamine; the latter two reagents presumably generated dimethylketene *in situ*.

(12) R. B. Woodward and G. Small, *J. Am. Chem. Soc.*, **72**, 1297 (1950).

(13) These pK_a values were calculated from points on the acid side of a standard potentiometric titration curve. Woodward and Small reported pK_a 2.8 for methylketene dimer.