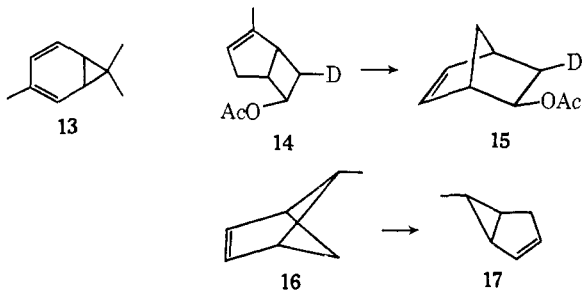
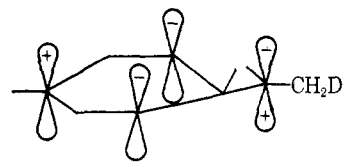
ence and the isotope effect) or by 0.1 Hz (the difference). The experimentally observed spectrum is the sum of these two spectra, and consists of three lines *ca.* 1.5 Hz apart in the intensity ratio 3:5:2. Trimethyltropilidene is *racemic*.[12]

The optical stability of bornadiene-*d* [82.6 mg, $[\alpha]_{365}$ −0.18° (*c* 10, C_6H_{12})] was demonstrated by recovering bornadiene-*d* (32 mg) from partial pyrolysis and observing the same specific rotation. The racemization must occur during the formation of trimethyltropilidene-*d*.

Transformation of bornadiene to 3,7,7-trimethyltropilidene surely proceeds *via* the as-yet-undetected caradiene **13** and is thereby another example of the rather rare 1,3 sigmatropic shifts.[13] Two selected cases, those of Berson[14] (**14** → **15**) and Roth[15] (**16** → **17**), maintain stereochemistry by means of a surprising inversion of configuration at the migrating carbon atom, while a 3-methyl derivative of **14**[16] and the epimer of **16** give products of somewhat randomized stereochemistry. By analogy, reasonable reaction paths for bornadiene consist of stretching the C-1–C-7 bond, then



either (a) rotating the geminal dimethyl group about its pivot several times, or (b) rotating the geminal dimethyl group only 90°, and finally forming the C-3–C-7 (or C-5–C-7) bond. The two possible modes a and b can probably be distinguished by determining the optical purity of the *p*-cymene formed in competition with the trimethyltropilidene. Lacking this experiment we can still speculate that the molecular arrangement b obtains.



Note well that the six electrons involved form a degenerate MO system and offer no way to control the concerted rearrangement. Bornadiene thermolysis is distinguished from the analogous 1,3 shifts by the presence of six, and not four, electrons, In this way, the occurrence of racemic trimethyltropilidene is completely rationalized.

Acknowledgment. The Varian HA-100 nmr instrument was purchased with a National Science Foundation Institutional Grant (Grant No. GP-3761), and the Perkin-Elmer Model 141 spectropolarimeter was purchased with funds awarded by a University of Houston Faculty Research Support Program Grant in Aid. Support of this work by the National Science Foundation is gratefully acknowledged.

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(12) The prediction of the intensities must take into account the isotopic and optical purity of the starting material and of the hydratropic acid. When this is done, the corrected ratio is 3.2:5.0:1.8 for racemic material and 5.1:1.2:2.8 or 1.7:8.0:0.6 for the two products of retained optical activity. Using reasonable error limits, our experimental ratio of 3.4:4.8:1.9 indicates 50 ± 5% of each epimer.

(13) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(14) J. A. Berson and G. L. Nelson, *J. Amer. Chem. Soc.*, **89**, 5503 (1967).

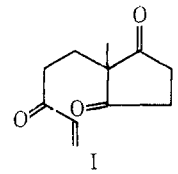
(15) W. R. Roth and A. Friedrich, *Tetrahedron Lett.*, 2607 (1969).

(16) J. A. Berson and G. L. Nelson, *J. Amer. Chem. Soc.*, **92**, 1096 (1970).

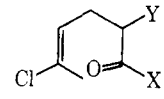
A Novel Construction of the Steroid Skeleton. The Utility of Di-*tert*-butyl Acetonedicarboxylate

Sir:

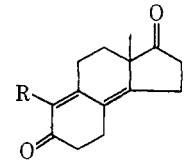
The potentialities of the enetrione I as a building block in steroid synthesis were recently suggested.[1]



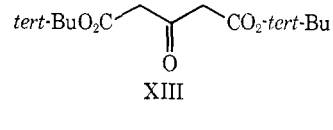
I



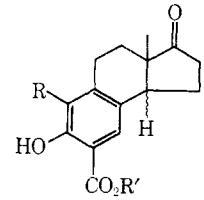
II, X = Me; Y = H
III, X = CH_2CO_2Me; Y = H
IV, X = Me; Y = CO_2Me
IX, X = OH; Y = H
X, X = Cl; Y = H
XI, X = $CH(Ac)CO_2$-*tert*-Bu; Y = H
XII, X = CH_2CO_2-*tert*-Bu; Y = H
XIV, X = CH_2CO_2-*tert*-Bu; Y = CO_2-*tert*-Bu



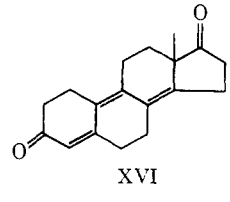
V, R = $CH_2CH{=}C(Cl)Me$
VII, R = Me
XV, R = CH_2CH_2Ac



XIII



VI, R = $CH_2CH{=}C(Cl)Me$; R′ = Me
VIII, R = Me; R′ = Et



XVI

In this communication we relate some new results which translate this possibility to practice.

Carbomethoxylation (sodium hydride–dimethyl carbonate–benzene) of compound II gave a 9:1 mixture

(1) S. Danishefsky and B. H. Migdalof, *J. Amer. Chem. Soc.*, **91**, 2806 (1969).

of β-keto esters, III[2] and IV.[2] Two-stage condensation ((i) 0.25 equiv of potassium *tert*-butoxide-*tert*-BuOH, room temperature, 48 hr; (ii) 1.8 equiv of TsOH–AcOH 90°, 3 hr) of III (purified by preparative glc) with I gave a mixture of trienedione V[2] (mp 94–95°; λ_{max}^{EtOH} 307 mμ (ε 18,200)) and salicylate VI[2,3] (mp 134–135°) in 39 and 14% yields, respectively.

Model experiments[4] in the propionylacetate series pointed to the method for avoiding unwanted salicylates such as VI, which arise from tautomerization of a tricyclic dienone intermediate[5-8] in which the β-keto ester arrangement has survived. Condensation of ethyl propionylacetate with I under the aforementioned conditions gave a mixture of VII[7] and VIII[2,3] (mp 96–96.5°). Identical condensation with *tert*-butyl propionylacetate gave only VII in 73% yield. Clearly the greater lability of the carbo-*tert*-butoxy group to the acidic cyclization conditions is a useful property in avoiding salicylate formation.

Accordingly, we prepared compound XII[2] starting with the unsaturated acid IX. Treatment of the latter with thionyl chloride gave the labile acid chloride X which served to acylate the sodium salt of *tert*-butyl-acetoacetate. Crude XI so produced was subjected to the action of ammonia to give keto ester XII (10% from IX). The value of the *tert*-butyl ester grouping is seen in that condensation of XII with enetrione I gave V in 56% yield with no evidence for aromatic by-products. These successes pinpoint the need for efficiently generated partners for condensation with I.

This objective was successfully realized. Treatment of 3-oxoglutaric acid with isobutylene under the following conditions (10 g of freshly prepared diacid, 1 ml of concentrated H_2SO_4, 100 ml of isobutylene shaken in a bomb at room temperature for 18 hr) gave XIII[9] in 90% yield. Monoalkylation of XIII (sodium hydride–THF–*trans*-1,3-dichloro-2-butene) gave XIV[2] in 64% yield. Two-stage condensation of keto diester XIV with I under the same conditions used for the monoesters gave V in 64% yield.[10,11] The objective of the smooth assemblage of an intermediate containing the requisite functionality for the elaboration of a wide variety of steroids has thus been reached.

Hydrolysis (concentrated H_2SO_4–methylene chloride, 0°, 0.5 hr) of V gave trienedione XV[2] (mp 146–147°; λ_{max}^{EtOH} 308 mμ (ε 17,200)) in 95%[12,13] yield. Base-catalyzed (3% KOH–dioxane–H_2O, 41–43°, 1 hr) cyclization of XV gave the tetracyclic XVI[14] in 68% yield. The latter has been converted[15] to 8[14]-dehydroestrone.

The power of this new methodology is seen in the fact that the overall conversion (*i.e.*, trisannelation) of 2-methylcyclopentane-1,3-dione to XVI is executed in 34% yield. The uses of compounds V and XV in the preparation of other steroids will be reported shortly.

Acknowledgments. This research was supported by Public Health Service Grant No. AM 08696-06. Nmr spectra were obtained by instrumentation supported by PHS Grant No. RR-00292-03.

(2) Combustion analysis within 0.3% of theory; infrared, nmr, and mass spectra are in full agreement with the proposed structure.

(3) Although its sharp melting point and nmr spectrum point to this being a homogeneous substance, the stereochemistry of the junction is unassigned.

(4) Conducted by B. H. Migdalof in these laboratories.

(5) While acid-catalyzed aromatization of dienones such as V is also precedented,[5] the rate of this process as distinct from the β-keto ester series is sufficiently slow as to allow for their survival under the acidic conditions of their formation.[1,7,8]

(6) C. Sannié and J. J. Panouse, *Bull. Soc. Chim. Fr.*, 1435 (1956).

(7) A. Frey, "Promotionsarbeit," E. T. H. Zurich, 1954.

(8) J. J. Panouse and C. Sannié, *Bull. Soc. Chim. Fr.*, 1429 (1956).

(9) For a recent but less convenient preparation of XIII see H. Paul and J. Polyczynski, *J. Prakt. Chim.*, **312**, 240 (1970).

(10) Also isolated from this reaction was a 10% yield of II which undoubtedly arises from acidic degradation of unreacted XIII. We were unable to detect any of the isomer of V containing the side chain on the α′ side of the dienone. This is another illustration[11] of the tendency of the monoalkylated derivative of acetonedicarboxylates to undergo base-induced alkylation at the methylene carbon.

(11) *Cf.* G. Schroeter, *Chem. Ber.*, **49**, 2711 (1916).

(12) The use of methylene chloride as diluent is responsible for this unusually high yield for an enol chloride → ketone transformation. The yield under the standard conditions[13] is 61% yield. We thank Dr. U. Eder of Schering AG (Berlin) for bringing this method to our attention.

(13) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965).

(14) T. B. Windholz, J. H. Fried, H. Schwam, and A. A. Patchett, *J. Amer. Chem. Soc.*, **85**, 1707 (1963).

(15) D. B. R. Johnson, D. Taub, and T. B. Windholz, *Steroids*, **8**, 365 (1966).

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Singlet Oxygen Analogs in Biological Systems. Coupled Oxygenation of 1,3-Dienes by Soybean Lipoxidase

Sir:

The formation of allylic hydroperoxides from alkenes with allylic hydrogens and the addition of oxygen to 1,3-dienoid systems are two well-established reactions of singlet molecular oxygen.[1] Similar processes of oxygenation have been postulated in enzyme-mediated reactions although direct evidence is still lacking. Soybean lipoxidase catalyzes the conversion of *cis,cis*-1,4-pentadienes to the hydroperoxides of *cis,trans*-1,3-dienes by molecular oxygen[2]—a process directly analogous to the action of singlet oxygen on alkenes. In the presence of its substrate (linoleic acid or its methyl or ethyl ester), this enzyme also catalyzes the coupled oxidation of carotene.[3] The possibility that the mode of catalysis by lipoxidase mimics the reactions of singlet oxygen is being investigated and results on the coupled oxygenation of 1,3-dienoid systems are reported here.

In general, 0.125 mmol of the dienoid compound[4] and 0.5 mmol of ethyl linoleate[5] are suspended in 1.5 l. of 0.05 *M* pH 9 Tris buffer. The incubation, which is carried out at 30° and in the dark, is initiated by the addition of the enzyme (240,000 units[6] or sufficient so that the reaction is complete in 1 hr). Thus, tetraphenylcyclopentadienone yielded its endoperoxide (I) (20%; uv and ir spectra identical with those of an

(1) C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968), and references cited therein.

(2) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **242**, 5329 (1967).

(3) R. T. Holman, *Arch. Biochem.*, **10**, 519 (1946).

(4) The choice of dienoid compounds is limited by the inability of most of such compounds to form a stable fine suspension in aqueous media.

(5) No reaction was observed in the absence of ethyl linoleate.

(6) As defined by the supplier (Sigma Co.).