(24% yield based on recovered starting material) consisted of a 17:83 mixture of **5** and **6** from which **6** was isolated by chromatography. Its nmr spectrum showed absorption for vinyl protons at τ 3.92–4.57 (2 H) as an AB quartet, α-hydroxy proton (1 H) at 6.2, carbomethoxy protons at 6.32 and 6.37 (6 H) as sharp singlets, and methylene and bridgehead protons as a broad multiplet from 7.1 to 8.5.

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.55; H, 6.36.

7,7-Dicarbomethoxycycloheptatriene (8).—To a mixture of the allylic alcohols (1.34 g, 5.90 mmol, 80% **5** and 20% **6**) dissolved in 20 ml of dry 2,6-lutidine was added dropwise at 0° a solution of 4.50 g (17.7 mmol) of *p*-bromobenzenesulfonyl chloride in 5 ml of 2,6-lutidine. After 20 hr at room temperature, the mixture was treated with 20 ml of water and extracted with ether. The extract was washed successively with 10% hydrochloric acid, water, and sodium bicarbonate solution, dried over sodium sulfate, and evaporated to give 692 mg of a viscous yellow oil. Chromatography on 20 g of Woelm basic alumina (activity IV) gave a total of 387 mg of partially crystalline material which consisted mainly of **8** contaminated with a few per cent of dimethyl phenylmalonate. Recrystallization from pentane–ether gave 322 mg of colorless prisms, mp 45–45.5°. The yield based on starting material (112 mg recovered) was 28%.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.54; H, 5.87.

The 60-Mc nmr spectrum in CCl_4 showed the C-2, C-3, C-4, and C-5 protons as a multiplet from τ 3.44 to 3.95, the C-1 and C-6 protons as an unresolved doublet from 4.90 to 5.30, and the six carbomethoxy protons as a sharp singlet at 6.37. The spectrum at $-35°$ is described in the discussion section.

3,7,7-Trimethylcycloheptatriene was formed when 1.3 g (9.9 mmol) of 3-carene was added to a solution of 2.27 g (10 mmol) of dichlorodicyanoquinone in 10 ml of dry ether, and the mixture was heated at reflux for 30 min. Ether was removed on a rotary evaporator. Pentane was added to the residue, the precipitated solid was filtered off and extracted with pentane in a soxhlet, and the filtrate was evaporated to give 0.83 g of material which nnr analysis showed to be about 90% 3,7,7-trimethylcycloheptatriene **10** contaminated with some 3-carene. Vapor chromatographic isolation gave pure **10**, which had an infrared spectrum identical with that of an authentic sample.[6]

Registry No.—**4**, 15833-41-7; **5**, 15833-42-8; **6**, 15833-43-9; **7**, 15833-44-0; **8**, 15833-45-1.

β,γ-Unsaturated Acids and Esters by Photochemical Isomerization of α,β Congeners[1,2]

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Conant Laboratory,[4] Harvard University,
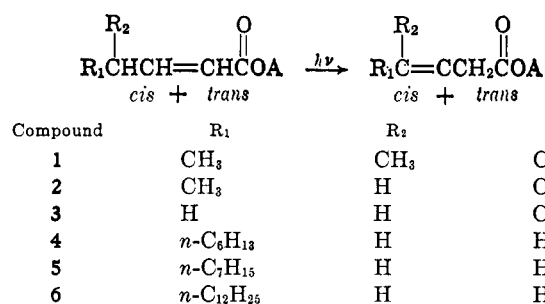*Cambridge, Massachusetts 02138*

β,γ-Unsaturated acids and esters have been less readily available than their α,β-unsaturated relatives, for which several convenient methods of synthesis are available.[5,6] Although it is well known that β,γ

isomers can be brought into equilibrium with their α,β congeners by catalysis with acid or base,[7] this method is based on thermodynamic control and suffers as a general synthetic method from wide variability with structure of the maximum attainable yield.

As a partial solution to the problem of synthesizing β,γ-unsaturated acids, we offer the photochemical isomerization of *acyclic* α,β-unsaturated acids or esters. This method is analogous to the related isomerization of α,β-unsaturated ketones and aldehydes.[8-12] The work also finds close parallels in the photochemical studies on the ionones[11] and in studies of the photochemical behavior of certain conjugated esters by Jorgenson.[13]

The conjugated acids and esters shown in Scheme I were irradiated as 2–5% solutions in saturated hydrocarbons, methanol, or in ethyl acetate with an un-

SCHEME I

$$
\underset{\substack{cis \;+\; trans}}{R_1\overset{\overset{\displaystyle R_2}{|}}{C}HCH=CH\overset{\overset{\displaystyle O}{\|}}{C}OA} \xrightarrow{h\nu} \underset{\substack{cis \;+\; trans}}{R_1\overset{\overset{\displaystyle R_2}{|}}{C}=CCH_2\overset{\overset{\displaystyle O}{\|}}{C}OA}
$$

Compound	R_1	R_2	A
1	CH_3	CH_3	C_2H_5
2	CH_3	H	CH_3
3	H	H	CH_3
4	$n\text{-}C_6H_{13}$	H	H
5	$n\text{-}C_7H_{15}$	H	H
6	$n\text{-}C_{12}H_{25}$	H	H

filtered 450-W Hanovia Type L lamp. Although the maximum absorption of the conjugated derivatives lies about 210 nm, there is still adequate absorption at 253.7 nm mercury line to permit the isomerization. With a Pyrex filter, which absorbs irradiation below 300 nm, there is no isomerization. Typical results are shown in Table I.

TABLE I

IRRADIATION OF α,β-UNSATURATED ACIDS AND ESTERS

Compd	Reacn time, hr	Solvent	cis/trans	% yield[a]
1	5	Pentane		85
2	5	Pentane	b	85
3	12	Pentane		20[c]
4	18	Pentane	0.5	94
5	18	Hexane	0.5	95[d]
6	18	Hexane	0.5	95[d,e]

[a] Based on starting material (% conversion). [b] Not determined. [c] Remaining material isolated as 50% methyl crotonate and 30% methyl isocrotonate. [d] Also carried out in methanol with similar results. [e] This experiment was conducted by Dr. S. Safe and is included here with his generous permission.

(1) Taken in part from the dissertation of R. R. Rando submitted in partial fulfillment of the requirements for the Ph.D. Degree, Yale University, Dec 1966.

(2) This work was supported in part by Research Grant GP-0959 to Yale University by the National Science Foundation.

(3) R. R. Rando expresses his gratitude to the National Institutes of Health for the award of a predoctoral fellowship, 1963–1966, and a postdoctoral fellowship (Harvard University), 1966–1967.

(4) Where inquiries should be addressed.

(5) E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. 1, Elsevier Publishing Co., Amsterdam, 1951, pp 624–626; W. S. Johnson, *Org. Reactions*, **1**, 252 (1942).

(6) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(7) See, for example, E. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935), and earlier references, or G. Kon, R. P. Linstead, and G. Maclennen, *ibid.*, 2454 (1932).

(8) N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).

(9) H. Wehrli, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta.*, **46**, 678 (1963).

(10) C. A. McDowell and S. S. Sifniades, *J. Amer. Chem. Soc.*, **84**, 4606 (1962).

(11) M. Mousseron-Canet, M. Mousseron, and P. Legendre, *Bull. Soc. Chim. Fr.*, 1509 (1961).

(12) K. J. Crowley, R. A. Schneider, and J. Meinwald, *J. Chem. Soc., Sect. C*, 571 (1966).

(13) M. J. Jorgenson, *Chem. Commun.*, 137 (1965).

The reaction proceeded approximately twice as rapidly in methanol as in the hydrocarbon solvents. In cases where *cis,trans* mixtures of the products were formed it was found that the esters could easily be separated by preparative tlc on $AgNO_3$–SiO_2 plates using 1% ether–hexane as the eluent. Since relatively large amounts of the *cis* products are formed, this synthetic route affords a reasonable method for obtaining the *cis* as well as the *trans* isomers.

Upon work-up virtually no remaining conjugated α,β-unsaturated isomers can be detected. When ethyl acetate was used as the solvent, not even trace amounts of the conjugated isomers could be detected (<0.1%) when the reaction was completed. Ethyl acetate, of course, filters out any light that the β,γ isomers might absorb. The high yield of unconjugated isomers depends on the fact that the integrated absorption of the unconjugated isomers above 200 nm is essentially zero while that of the conjugated isomers, if weak by customary standards, is much greater.[14]

In a reasonable mechanism, similar to that proposed by Yang and Jorgenson[8] for the photochemical isomerization of α,β-unsaturated ketones, it is hypothesized that the γ-hydrogen atom migrates to the carbonyl oxygen by means of an intramolecular, pseudo-cyclic transition state. This hypothesis requires the availability of the *cis*-geometrical isomer. That this requirement can be satisfied photochemically is shown in the study of ethyl 4-methyl-2-pentenoate, in which photochemical interconversion of the *trans* and *cis* isomers occurs more rapidly than the formation of the β,γ
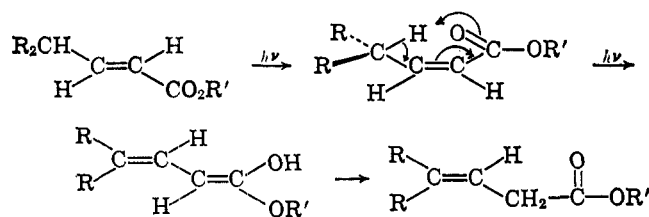
SCHEME II

isomer. Scheme II illustrates only the type of geometrical requirement imposed on the reaction. Whether a two-electron concerted process or a radical intermediate is involved is not known.

This hypothesis leads to the prediction that examples in which a prior isomerization of *trans* isomer to *cis* is hindered or impossible, the reaction should proceed at a very slow rate, if at all. This prediction is borne out in an experiment in which methyl 1-cyclohexenecarboxylate is found to be completely inert to photoisomerization. In this system a *cis* transition state would require the introduction of a prohibitively strained *trans* double bond into a six-membered ring. How inviolate this restriction will turn out to be must await further testing. It should be pointed out that the restriction does not appear to apply to α,β-unsaturated ketones; at least not in the example uncovered by Wehrli, *et al.*[9]

(14) H. H. Jaffé and M. Orchin, "Theory and Practice of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 218–219.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60 analytical nmr spectrometer. The spectra were taken in carbon tetrachloride solutions. The *cis,trans* mixtures of the β,γ-methyl esters were separated by preparative tlc on 10% silver nitrate–Adsorbosil I (SiO_2) with 1% ether–hexane as the eluent. Excellent separations of the conjugated from the nonconjugated esters could be effected with either a 5-ft, 20% silicon oil column (SF 96) on 60–80 mesh firebrick or on a 4-m, 15% diethylene glycol succinate on a 40–60 mesh Kieselguhr column. As the reaction times and work-up procedures utlized in the preparations of the 3-decenoic acids, 3-undecenoic acids, and 3-hexadecenoic acids were identical, only one procedure is included. The photolyses were conducted with an unfiltered Hanovia Type L lamp at room temperature. It should be noted that the reaction times are quite dependent on the age of the lamp in use. For example, *trans*-2-decenoic acid could be completely converted into the Δ^3 isomers in 2 hr with a brand new lamp.

Photolyses. A. Ethyl 4-Methyl-2-pentenoate.—A mixture of the *cis* and *trans* isomers (*trans* predominant) was synthesized by the method of Wadsworth and Emmons.[6] The esters (1.5 g, 0.011 mol) were dissolved in 125 ml of pentane in a 150-ml Pyrex well. A Hanovia quartz immersion well with a Type L lamp was set in place and the photolysis was commenced at room temperature. An aliquot of the reaction mixture was removed after 2 hr of reaction time and analyzed by glpc (silicon oil column, column temperature = 120°). A striking buildup of the *cis* conjugated ester was observed to occur. The reaction was terminated after a total of 5 hr of reaction time. The pentane was removed affording 1.3 g (86% of theoretical yield) of a liquid whose nmr and infrared spectra completely identified it as the β,γ-unsaturated ester. Distillation of this material afforded 1.2 g of the ester without leaving behind noticable polymeric residue. The reaction product was shown to be homogeneous by glpc analysis. The compound showed infrared absorption at γ_{CCl_4}, 738 cm^{-1} and nmr absorption at 8.28 (s of relative area 3), 8.40 (s of relative area 3), 4.75 (m of relative area 1), and 7.1 ppm (d of relative area 2) on the τ scale.

B. Methyl 2-Pentenoate.—A synthetic mixture of *cis*- and *trans*-methyl 2-pentenoate[6] was photolyzed as described above to afford the methyl 3-pentenoates in the yield reported. The products were identified by their nmr and infrared spectra: γ_{CCl_4}, 3040, 1740 cm^{-1}; nmr bands, 4.3 (m of relative area 2), 6.37 (s of relative area 3), 7.1 (m of relative area 2), and 8.32 ppm (m of relative area 3).

C. Methyl Crotonate.—Methyl crotonate (2.5 g, 0.025 mol) was dissolved in 220 ml of dry pentane and photolyzed in the normal manner for 12 hr.[15] The pentane was removed leaving 2.1 g (0.021 mol) of a faint yellow liquid. Vapor phase chromatography of this material on the silicon oil column showed the presence of three compounds isolated in the ratios of 2.5:1.4:1.0. The major product proved to be the unreacted starting material. The intermediate proved to be the *cis* isomer, methyl isocrotonate, and the minor product proved to be the β,γ-unsaturated isomer, methyl 3-butenoate. Methyl isocrotonate was identified by comparison with authentic material, whereas methyl 3-butenoate was identified by its infrared and nmr spectra: γ_{CCl_4}, 1745 cm^{-1}; nmr, 4.3 (m of relative area 1), 4.8 (m of relative area 1), 5.05 (m of relative area 1), 6.4 (s of relative area 3), and 7.1 ppm (d of relative area 2).

D. Methyl 1-Cyclohexenecarboxylate.—Methyl 1-cyclohexenecarboxylate was synthesized by the method of Fichter and Simon.[16] Photolysis of the ester (3.0 g, 0.021 mol) in 220 ml of pentane in the usual manner for 7 hr afforded 2.8 g, 0.02 mol of starting material as deduced from its homogeneity on the silicon oil and diethylene glycol succinate columns and its infrared and nmr spectra.

E. *trans*-2-Decenoic Acid.—Commercial *trans*-2-decenoic acid (Aldrich Chemical Co.) (4.0 g, 0.021 mol) was dissolved in 220 ml of pentane and photolyzed in the usual manner for 18 hr. Removal of the solvent afforded 3.95 g of a colorless oil whose nmr and infrared spectra identified it as being the β,γ-unsaturated ester(s). An aliquot of this material was esterified with diazomethane. The methyl esters were analyzed on the silicon oil

(15) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).
(16) F. Fichter and C. Simon, *Helv. Chim. Acta*, **17**, 1218 (1934).

column at column temperature of 120°. One major peak was observed having the same retention time as an independently synthesized mixture[17,18] of the *cis-* and *trans-β,γ* esters. A peak amounting to 1% of the *β,γ* peak was also observed having the same retention time as the *trans-α,β* ester. When the photolysis was run in ethyl acetate this peak was not observed. That the main peak was indeed a mixture of the *trans-* and *cis-β,γ* isomers was shown by preparative tlc on AgNO₃–SiO₂ eluting several times with 1% ether–hexane. The *trans-β,γ* predominated by a factor of 2 over the *cis* and traveled closest to the solvent front. Both isomers were identified by comparing their infrared spectra with those of authentic samples, prepared independently.

Registry No.—1 (*cis*), 15790-85-9; 1 (*trans*), 15790-86-0; 2 (*cis*), 15790-87-1; 2 (*trans*), 15790-88-2; 3 (*cis*), 4358-59-2; 3 (*trans*), 623-43-8; 4 (*cis*), 15790-91-7; 4 (*trans*), 334-49-6; 5 (*cis*), 15790-93-9; 5 (*trans*), 15790-94-0; 6 (*cis*), 2825-68-5; 6 (*trans*), 929-79-3.

(17) M. Newman and J. J. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1292 (1949).

(18) R. P. Linstead, E. G. Noble, and E. J. Boorman, *J. Chem. Soc.*, 557 (1933).

A Concomitant Ethinylation and Esterification Reaction

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The preparation of 10β-hydroperoxy steroids, such as 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one (I, R = H), has been reported from these laboratories.[1] Tests in rats have shown that I (R = H) is a potent contraceptive agent acting by a novel biological mechanism.[2] In view of the marked anti-conception activity ascribed to ethynodiol diacetate (VI)[3] and ethindrone acetate (V, R = CH₃CO),[4] both containing a 17β-acetoxy function, it was decided to prepare the ester analog of I (R = H).

The process used for the preparation of I (R = H) (see Scheme I) was considered to be adaptable for the preparation of I (R = CH₃CO). However, neither 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol (III, R = H) nor 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one (IV, R = H) were found to be useful substrates for acetylation. Although the 17β-tertiary hydroxy was relatively easily esterifiable by hot acetic anhydride[5] or by acetic anhydride with acid catalysis,[6] the reactive 3-keto-Δ⁵⁽¹⁰⁾ system in IV (R = H), essential for the hydroperoxidation, and the diene

system in III (R = H) underwent unwanted isomerization.[7]

Accordingly, we chose to investigate alternate procedures in the sequence for the formation of the 17β-acetoxy,17α-ethinyl moiety.

The formation of this moiety during the ethinylation reaction of the ketone II appeared possible since an oxyanion may be considered to be a generated species and might be available for rapid acylation.
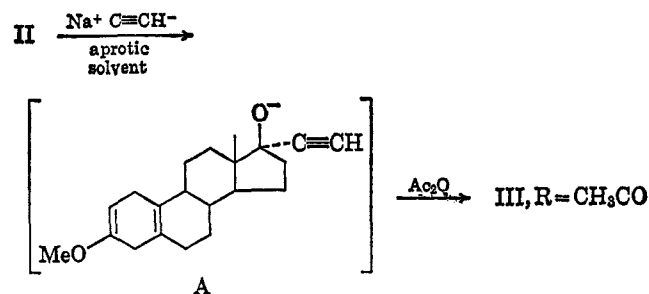
Various solvent systems are known for carrying out the ethinylation of ketones; these include liquid ammonia and *t*-butyl alcohol. We considered that a preferred solvent system would be one wherein the availability of protons was low or nonexistent so that the solvent would react at a slow rate, if at all, with the esterification reagent and discharge at a slow rate, if at all, the oxyanion of "A." Dimethylformamide was considered to be such a solvent.[8]

Accordingly, II was treated with sodium acetylide[9] in dimethylformamide at room temperature. After 15 min, acetic anhydride was added to the reaction medium. After an additional minute, isolation of the reaction product afforded an excellent yield of 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-acetate (III, R = CH₃CO). This concomitant esterification could also be accomplished with tetrahydrofuran as the solvent.[10] In our opinion, this method constitutes a facile procedure for the esterification of the important steroid hormone class which bears the 17β-OH-17α-alkinyl grouping.

Proof of structure of III (R = CH₃CO) was effected by conversion of III (R = CH₃CO) with oxalic acid into 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH₃CO) which then, with hydrochloric acid, was converted into the known 17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (V, R = CH₃CO).[11]

In view of the ready esterification *via* the presumed species "A," it was felt that this same species could also be made available for esterification by base treatment of III (R = H). However, when III (R = H) was treated with potassium *t*-butoxide in dimethylformamide and then with acetic anhydride, the ethinyl

(1) (a) E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964); (b) U. S. Patent 3,280,157 (Oct 18, 1966).

(2) (a) A. S. Watnick, J. Gibson, M. Vinegra, and S. Tolksdorf, *J. Endocrinol.*, **33**, 241 (1965); (b) A. S. Watnick, S. Tolksdorf, J. Kosierowski, and I. A. Tabachnick, Excerpta Medica International Congress Series No. III, IInd International Congress on Hormonal Steroids, Milan, May 23–28, 1966, Paper No. 123.

(3) G. Pincus, C. R. Garcia, M. Paniagua, and J. Shepard, *Science*, **138**, 439 (1962).

(4) E. Meers, *Intern. J. Fertility*, **9**, 1 (1964); H. C. Walser, R. R. Margulis, and J. E. Ladd, *ibid.*, **9**, 189 (1964).

(5) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943). In these references the configuration of the hydroxy function is β.

(6) I. Iriate, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 436 (1959).

(7) The formation of III (R = CH₃CO) from III (R = H) using acetic anhydride and pyridine is reported in British Patent 922,877 (April 3, 1963), although no physical constants are noted. In our hands the procedure was unsatisfactory because of substantial loss of the diene system in ring A.

(8) C. Burgess, D. Bunn, P. Feather, M. Howarth, and V. Petrow [*Tetrahedron*, **22**, 2829 (1966)] report etherification with methyl iodide in a soda-mide–liquid ammonia medium.

(9) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Amer. Chem. Soc.*, **80**, 4717 (1958).

(10) We wish to thank R. Grocela and N. Murrill of the Process Research Development Department for carrying out this experiment.

(11) Compare ref 6, wherein V (R = CH₃CO) was prepared from V (R = H) by acid esterification to 17α-ethinyl-3,5-estradiene-3,17-diol 3,17-diacetate followed by acid hydrolysis.