Notes

Enamine Chemistry. III. The Reaction of Ketene Acetals, O,N-Acetals, and N,N-Acetals with Acetylenic Esters

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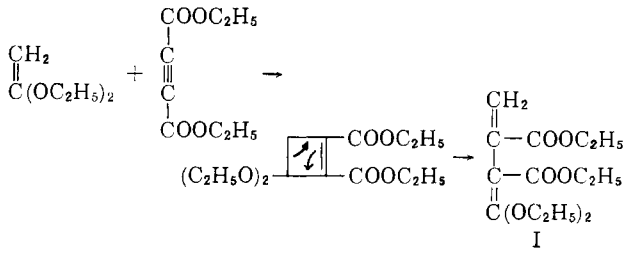
The reaction of enamines with acetylenic esters has been reported.[1] It appeared of interest to determine whether the closely related ketene acetals, O,N-acetals, and N,N-acetals would undergo similar reactions with acetylenic esters, and this indeed proved to be the case.

The products derived from the reaction of ketene acetals with acetylenic esters are those arising from the cyclobutene rearrangement of the initially formed cycloaddition products. This is illustrated for the reaction of ketene diethyl acetal with diethyl acetylenedicarboxylate.



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McElvain[2] previously had reported the reaction of excess ketene diethyl acetal with diethyl acetylenedicarboxylate under rather drastic conditions (*i.e.*, 195° for 24 hr.) to lead in poor yield to a product ultimately converted to 3,5-diethoxyphthalic acid. It appears reasonable that McElvain's product could have arisen from a Diels–Alder addition of I and another mole of the ketene acetal.

Experimental[3]

Materials.—1-Ethoxy-N,N-dimethylvinylamine was prepared by the method of Meerwein[4] except that one equivalent of alcohol-free sodium ethoxide suspended in ether was used in place of excess ethanolic sodium ethoxide. Yields of 73% and 70% were obtained in runs of 1 and 3 moles, respectively.

1,1-Dipiperidinoethylene was prepared by the method of Baganz and Domaschke.[5] Ketene diethyl acetal[6] and dimethylketene dimethyl acetal[7] were prepared as described by McElvain.

Ketene Diethyl Acetal with Diethyl Acetylenedicarboxylate.—Diethyl acetylenedicarboxylate (29.2 g., 0.17 mole) was added to a mixture of ketene diethyl acetal (20 g., 0.17 mole) and acetonitrile (50 ml.). The addition was made rapidly over a 4-min. period and the temperature of the reaction mixture rose to a maximum of 66° after 8 min. After standing for 1.5 hr., the mixture was distilled through a 4-in. Vigreux column to give, after removal of a 12-g. forerun, 26 g. (53%) of diethyl 2-(diethoxymethylene)-3-methylenesuccinate, b.p. 116–120° (*ca.* 0.5 mm.), $n^{20}D$ 1.4741.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.8; H, 7.7. Found: C, 58.8; H, 7.8.

To diethyl 2-(diethoxymethylene)-3-methylenesuccinate (5 g., 0.017 mole) was added water (5 ml.), ethyl alcohol (5 ml.), and concentrated hydrochloric acid (1 drop). The temperature of the resulting mixture rose immediately to 38°. After 5 min., the mixture was heated to 55° on the steam bath. A solution of potassium hydroxide (5 g., 0.09 mole) in water (10 ml.) was added and the mixture was heated for 1 hr. on the steam bath at 80–85°. It was then made acidic with concentrated hydrochloric acid (10 ml.) and heated an additional hour. The mixture was then cooled and extracted twice with an equal volume of ether. Evaporation of the ether on the steam bath left 1.7 g. (75%) of crude itaconic acid, which was recrystallized once from an ethyl acetate–hexane mixture to give 1.3 g. (57%), m.p. 165–166°. The infrared spectrum of the material was identical with that of an authentic sample.

Dimethylketene Dimethyl Acetal with Dimethyl Acetylenedicarboxylate.—Dimethylketene dimethyl acetal (38.6 g., 0.33 mole) and dimethyl acetylenedicarboxylate (47.3 g., 0.33 mole) were combined and refluxed for 2 hr. and 10 min. Distillation of the reaction mixture through a 6-in. Vigreux column gave 51 g. (59%) of dimethyl 2-(dimethoxymethylene)-3-isopropylidenesuccinate, b.p. 95–110° (*ca.* 0.5 mm.), $n^{20}D$ 1.4978.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 56.1; H, 7.1.

Dimethyl 2-(dimethoxymethylene)-3-isopropylidenesuccinate (25.8 g., 0.1 mole) was combined with water (25 ml.) and methanol (25 ml.) containing 2 drops of concentrated hydrochloric acid. The mixture was refluxed for 30 min. and then distilled through a 6-in. Vigreux column to give, after removal of the methanol and water, 21.5 g. (88%) of dimethyl 2-isopropylidene-3-methoxycarbonylsuccinate, b.p. 96–103° (0.5–0.7 mm.), $n^{20}D$ 1.4701.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.2; H, 6.6. Found: C, 54.4; H, 6.8.

Dimethyl 2-isopropylidene-3-methoxycarbonylsuccinate (20 g., 0.082 mole) was combined with a solution of potassium hydroxide (25 g., 0.45 mole) in water (50 ml.). An insoluble salt was formed and the mixture was diluted to 250 ml. to give a homogeneous solution which was heated under reflux for 2 hr. The solution was then acidified with concentrated hydrochloric acid (50 ml.) and heated on the steam bath for 1 hr. The solution was chilled and the solid which separated was collected and dried in the vacuum oven to give 9.1 g. (70%) of crude teraconic acid, m.p. 171–172.5°. A sample of this was recrystallized from water, m.p. 174–175°. The infrared spectrum of the material was identical with that of authentic teraconic acid.

Dimethylketene Dimethyl Acetal with Methyl Propiolate.—Dimethylketene dimethyl acetal (28 g., 0.24 mole) and methyl propiolate (20 g., 0.24 mole) were combined and heated under reflux for 20 hr., during which time the temperature of the reaction mixture rose from 101° to 169°. Distillation of the reaction mixture through a 6-in. Vigreux column gave 23 g. (42%) of methyl 2-(dimethoxymethylene)-4-methyl-3-pentenoate, b.p. 72–75° (*ca.* 1 mm.), $n^{20}D$ 1.4903.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.9; H, 8.1. Found: C, 59.7; H, 8.0.

1-Ethoxy-N,N-dimethylvinylamine with Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (28.4 g., 0.2 mole) was added to a solution of 1-ethoxy-N,N-dimethylvinylamine (23 g., 0.2 mole) in 50 ml. of ether at a rate such as to

(1) Paper II of this series: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(2) S. M. McElvain and H. Cohen, *J. Am. Chem. Soc.*, **64**, 260 (1942).

(3) Boiling points and melting points are uncorrected. Melting points were determined using a Fisher-Johns apparatus.

(4) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.*, **641**, 1 (1961).

(5) H. Baganz and L. Domaschke, *Chem. Ber.*, **95**, 2095 (1962).

(6) S. M. McElvain and D. Kundiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 506.

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maintain the mixture at reflux. The solution was then heated under reflux for 1 hr. and distilled to give 30 g. (58%) of dimethyl 2-[(dimethylamino)(ethoxy)methylene]-3-methylenesuccinate, b.p. 121–124° (0.5 mm.), $n^{20}D$ 1.5270.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.5; N, 5.5. Found: C, 56.1; H, 7.5; N, 5.5.

1,1-Dipiperidinoethylene with Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (7.8 g., 0.055 mole) was added in portions to 1,1-dipiperidinoethylene (10.6 g., 0.055 mole) in 25 ml. of ether with cooling to keep the temperature at 25–30°. Chilling and filtration of the reaction mixture gave 15 g. (82%) of dimethyl 2-(dipiperidinomethylene)-3-methylenesuccinate, m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.3; H, 8.4. Found: C, 64.6; H, 8.6.

Determination of the Configuration of C-9 in Levopimaric Acid[1]

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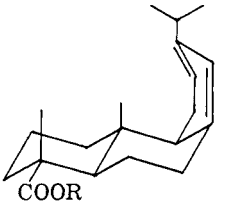
Although the gross structure of levopimaric acid has been well known for many years,[3] the stereochemistry of the material is known with less certainty. The absolute steric arrangement of C-4, C-5, and C-10 (steroid numbering) was established by conversion of levopimaric acid to abietic acid which, in turn, has been related to lanosterol.[4,5] In agreement with these results is the more recent work relating pimaric acid, which has been related to abietic acid,[6,7] to cholesterol.[8]

The configuration of C-9 in levopimaric acid has been more difficult to determine with certainty because the position is allylic to the reactive diene system and most interconversion studies have involved acid-catalyzed reactions. If the stereochemistry of this center were the less stable arrangement, these chemical studies might well have led to inversion of the center. Nevertheless, much chemical evidence has been presented in favor of an *anti*-backbone for levopimaric acid. For the most part the α-configuration at C-9 has been assigned by correlation with abietic and neoabietic acids,[9–11] the configuration in the latter materials having been assigned on the basis of conformational concepts and rotatory dispersion studies.[3,12,13] Recent investigations of the maleic anhydride adduct of levopimaric acid[14] also were best interpreted by assuming a C-9 α-configuration.

Purely physical methods also have been employed by various workers interested in this stereochemistry question. By comparison of the molecular rotations of levopimaric acid and $\Delta^{2,4}$-cholestadiene, it was concluded that the C-9 hydrogen has a β-orientation.[12] More recently it has been established that the direction of the skew of the diene rather than the configuration of the allylic center determines the sign of the Cotton curve of an optically active cyclohexadiene.[15] Using this concept, it was concluded that, if levopimaric acid did possess a 9α-configuration, the diene containing ring must assume a folded conformation (I) rather than the expected extended form II.[15] Surface film measurements were well in accord with this hypothesis.[16]

With such an accumulation of data, the α-assignment at C-9 appears preferable. However, since a rather unusual conformation is required to explain the dispersion curve, an unequivocal determination would



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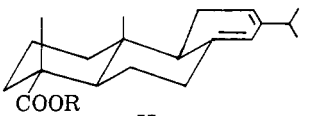

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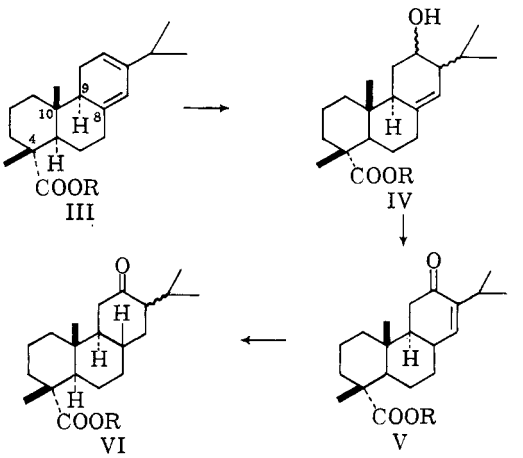
be desirable. In the course of another study, we have obtained the unsaturated keto ester V which has permitted settlement of this stereochemistry problem.



Selective hydroboration of methyl levopimarate (III) with disiamylborane[17] gave mainly one unsaturated alcohol (IV) in 40% yield. Oxidation of IV to the ketone followed by base-catalyzed isomerization of the double bond into the α,β position afforded the conjugated isomer V. Hydrogenation of V yielded the saturated ketone VI which showed a positive Cotton curve.[18] Application of the Octant Rule showed that only with a *trans* 8β,9α B/C ring fusion would

(1) This work was supported in part by grant no. A-709, U. S. Public Health Service.

(2) National Science Foundation Cooperative Predoctoral Fellow, 1960–1962.

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(18) We are indebted to Professor C. Djerassi for determination of the optical rotatory dispersion curve.