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Thermal Condensation of α-Keto Esters with Olefins

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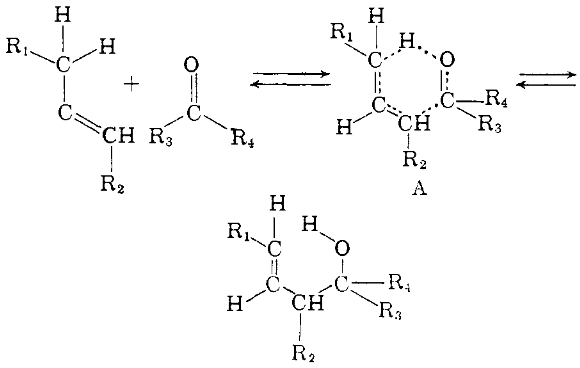
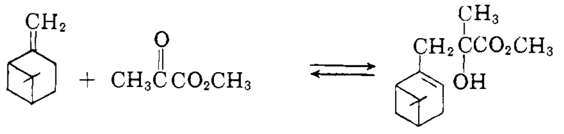
β-Pinene and allylbenzene each condense thermally with methyl pyruvate to 1–1 adducts which are α-hydroxy esters, and the reaction is highly stereoselective. These adducts, as well as the commercially available β-hydroxyolefin, nopol, upon heating under appropriate conditions regenerate the components from which they were formed originally. All of the data for this reversible process are best rationalized in terms of a concerted mechanism involving a six-membered cyclic transition state.

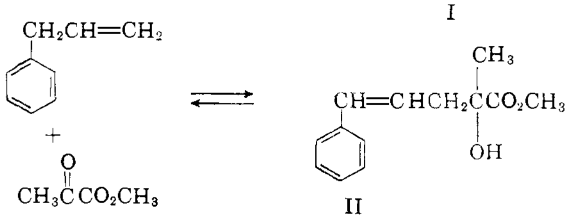
Monoölefins react thermally with a variety of dienophiles[3,4] and reactive aldehydes, such as formaldehyde[5] and chloral,[6] to form 1–1 adducts whose structures are easily rationalized in terms of a reaction involving a six-membered cyclic transition state.[4] The same transition state (A) has been proposed[7,8] to explain the pyrolytic decomposition of β-hydroxyolefins which yields olefins and carbonyl compounds. In the present study, we have clearly established the reversibility of this reaction and believe the following general expression to be valid. Although specific examples of the forward reaction thus far recorded involve only the interaction of olefins with aldehydes, we have now shown that ketones possessing quite reactive carbonyl groups may also be employed.



In this paper we wish to report that methyl pyruvate reacts thermally with β-pinene and allylbenzene to form the expected α-hydroxy esters I and II, respectively.



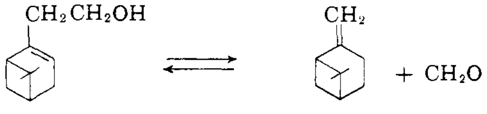
I



II

Compound I was isolated in a yield of 55% when a solution of methyl pyruvate in excess β-pinene was heated under reflux at 165°, and this yield was not increased by extending the heating period beyond 96 hours, in spite of the fact that methyl pyruvate was still present. When a solution of the adduct I in β-pinene was heated under reflux for 72 hours, methyl pyruvate was readily separated from the resulting mixture and adequately characterized.

No attempt was made to bring about the slow thermal decomposition of the adduct II at relatively low temperatures, but this substance was rapidly decomposed when passed through a hot tube (500°),[7] and both allylbenzene and methyl pyruvate were identified among the products formed. Nopol (III)[5] is prepared commercially from the thermal condensation of β-pinene and formaldehyde. We have now shown that a solution of III in tetralin when heated at 198° liberates formaldehyde slowly in accordance with the equation



III

These experiments appear to demonstrate clearly the reversibility of the thermal condensation of olefins with aldehydes or ketones.

An examination of the molecular models of β-pinene and methyl pyruvate indicates that the appropriate cyclic transition state (A) can be formed most readily (*i.e.*, with a minimum of nonbonded repulsion) when the ester approaches the olefin from the methylene-bridge side and with its large carbomethoxyl group directed away from the hydrocarbon moiety. These considerations, coupled with our earlier experimental results,[4] led to the prediction that the reaction giving rise to I should be highly stereoselective, and that one of the two possible diastereoisomers should predominate. This, indeed, proved to be the case. When the optically active adduct I or its dihydro derivative, formed by stereospecific hydrogenation,[9] were subjected to careful gas phase chromatographic studies, no resolution into diastereoisomers could be detected. The essential homogeneity of I was confirmed by an even more crucial experiment. The potassium salt, formed from the saponification of I, was purified by multiple recrystallizations from ethyl acetate, converted to the corresponding acid, and the latter was then

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(1) Alfred P. Sloan Research Associate.

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(3) K. Alder, F. Pascher and A. Schmitz, *Ber.*, **76**, 27 (1943).

(4) R. T. Arnold and J. S. Showell, THIS JOURNAL, **79**, 419 (1957).

(5) J. P. Bain, *ibid.*, **68**, 638 (1946).

(6) M. Vilkas, G. Dupont and R. Doulon, *Bull. soc. chim. France*, 799 (1955).

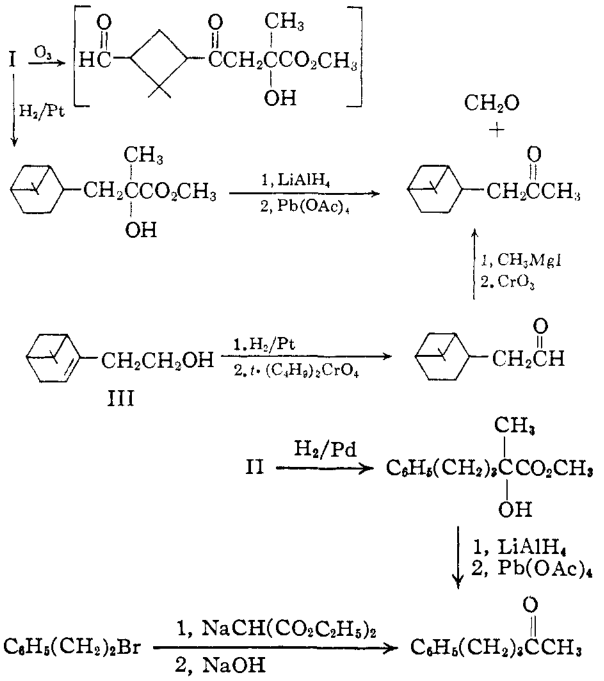
(7) R. T. Arnold and G. Smolinsky, THIS JOURNAL, **81**, 6443 (1959).

(8) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, **25**, 129 (1960).

(9) G. W. Eigenmann and R. T. Arnold, THIS JOURNAL, **81**, 3440 (1959).

esterified with diazomethane. The physical properties of the substance so obtained, compared very favorably with those of the original adduct I. If the product I had contained any appreciable quantity of a second optical isomer, a quite different result could have been anticipated.

The formulas assigned to the adducts I and II are based upon our conception of the manner in which they are formed, and these structures are completely consistent with the spectral data. Final confirmation, however, rests upon the chemical transformations outlined



Experimental

Thermal Condensation of β-Pinene with Methyl Pyruvate.—Preliminary experiments indicated that heating methyl pyruvate in an excess of boiling β-pinene represented a better method of effecting this condensation than refluxing equivalent quantities of the reactants in xylene as solvent.

A solution of methyl pyruvate[10] (30.6 g.), hydroquinone (0.1 g.) and β-pinene (408 g.) was maintained under reflux for 96 hours. The excess β-pinene was removed under reduced pressure and gave a positive test for methyl pyruvate with 2,4-dinitrophenylhydrazine. Fractionation of the viscous reaction product gave the adduct I, methyl 2'-hydroxy-2'-methyl-3'-6,6-dimethylbicyclo[3,1,1]hept-2-en-2-ylpropionate, (39.4 g., 55%), b.p. 88–89° (0.5 mm.), n^{25}_D 1.4800, $[\alpha]^{25}_D$ −30.2°. A brown residue (11.2 g.) from this distillation was not characterized.

The product showed strong hydroxyl and carbonyl bands at 2.95 and 5.81 μ, decolorized bromine and rapidly reduced potassium permanganate. Its vapor phase chromatogram obtained with a 10' polyester column (160°, helium pressure 12 lb.) showed a single peak, R_t 49 min.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.65; H, 9.14.

The adduct I (4.76 g.) was reduced quantitatively at room temperature with hydrogen (40 lb. pressure) and platinum oxide (0.1 g.) in ethanol (20 ml.) to give methyl-2'-hydroxy-2'-methyl-3'-*cis*-6,6-dimethylbicyclo[3,1,1]-heptan-2-ylpropionate, b.p. 95–96° (0.4 mm.), n^{25}_D 1.4785, $[\alpha]^{26}_D$ −19.3°.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.98; H, 10.08. Found: C, 69.88; H, 10.19.

This material had absorption bands at 2.95 and 5.84 μ expected for the hydroxy ester. Its vapor phase chromatogram showed a single peak both with a 5' silicone column (160°, helium pressure 12 lb., R_t 52 min.) and a 10' polyester column (160°, helium pressure 12 lb., R_t 82 min.).

Proof of Structure of Adduct I.—The adduct (6.21 g.) was hydrogenated as described above and the dihydro derivative freed from the last traces of ethanol. This residue, dissolved in tetrahydrofuran (50 ml.), was reduced with a solution of lithium aluminum hydride (1.5 g.) in tetrahydrofuran (160 ml.) at 25° during the course of 12 hours. Excess reducing agent was decomposed by slow addition of water, sulfuric acid (4 *N*) was added to dissolve the aluminum hydroxide, the mixture was extracted with ether and the latter solution evaporated to yield the crude glycol which showed an infrared band at 3.04 μ. The undistilled glycol was dissolved in aqueous acetic acid (100 ml., 50%) and oxidized with lead tetraacetate (11.6 g.) in glacial acetic acid (150 ml.). Sulfuric acid (4 *N*) was added dropwise to precipitate lead sulfate, and the filtrate was poured into ice-water and neutralized with sodium carbonate solution. Ether extraction followed by distillation of the ether layer gave 1'-*cis*-6,6-dimethylbicyclo[3,1,1]heptan-2-yl-2'-propanone (2.93 g., over-all yield 63.5%), b.p. 125–126° (19 mm.), n^{25}_D 1.4765.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.94; H, 11.29.

This ketone has an absorption band at 5.90 μ and gave a 2,4-dinitrophenylhydrazone, m.p. 101° (methanol).

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: N, 15.55. Found: N, 15.30.

The aqueous solution from the above ether extraction was heated and the evolved gas was bubbled through a solution of 2,4-dinitrophenylhydrazine. The precipitate (m.p. 167.5°) proved to be identical with formaldehyde 2,4-dinitrophenylhydrazone.

***cis*-6,6-Dimethylbicyclo[3,1,1]heptan-2-ylacetaldehyde.**—A solution of *t*-butyl chromate (prepared from 26.4 g. of chromic oxide and 100 ml. of *t*-butyl alcohol) in anhydrous benzene (150 ml.) was added dropwise, with stirring, to 2'-*cis*-6,6-dimethylbicyclo[3,1,1]heptan-2-ylethanol (33.6 g.) dissolved in dry benzene (150 ml.). Stirring of this mixture was continued for 8 hours. Oxalic acid (10 g.) and sulfuric acid (100 ml., 4 *N*) were added, and the mixture was exhaustively steam distilled. The benzene layer, so obtained, was separated, dried and distilled to give the product (15.6 g., 47%), b.p. 103–104° (13 mm.), n^{25}_D 1.4795.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.43; H, 10.91. Found: C, 79.48; H, 10.96.

This aldehyde showed the expected absorption bands at 3.71 and 5.80 μ and readily formed a 2,4-dinitrophenylhydrazone, m.p. 143.5°.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: N, 16.17. Found: N, 16.09.

1'-*cis*-6,6-Dimethylbicyclo[3,1,1]heptan-2-yl-2'-propanol.—The acetaldehyde derivative described above (8.3 g.) dissolved in dry ether (25 ml.) was allowed to react for 1 hour with a Grignard solution prepared from magnesium (1.34 g.), methyl iodide (7.76 g.) and ether (100 ml.). After decomposition of the reaction mixture with ammonium chloride solution (50 ml., 25%), the product was isolated in the usual manner; yield 7 g. (77%), b.p. 77–78° (0.3 mm.), n^{25}_D 1.4850.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.05; H, 12.17. Found: C, 79.16; H, 12.05.

1'-*cis*-6,6-Dimethylbicyclo[3,1,1]heptan-2-yl-2'-propanone.—Chromic oxide (7.5 g.) was added with stirring to dry pyridine (75 ml.) held at 30°. To this solution was added the above propanol derivative (6.8 g.) dissolved in pyridine (70 ml.), and the mixture was stirred at room temperature for 24 hours and steam distilled. Acidification of the steam distillate followed by extraction of the mixture with ether and distillation of the ethereal layer gave the expected ketone (5.45 g., 81%), b.p. 125–126° (20 mm.), n^{25}_D 1.4765.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.66; H, 11.42.

The infrared spectrum and 2,4-dinitrophenylhydrazone derivative (m.p. 101°) of this ketone were identical with those of the ketone obtained above from the degradation of adduct I.

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[10] R. O. Clinton and S. C. Laskowski, This Journal, **70**, 3135 a (1948).

Ozonization of Adduct I.—Ozone was bubbled through a solution of the adduct (2.38 g.) in ethyl acetate (25 ml.) at −70° until the reaction was completed. The solvent was removed under reduced pressure, and the liquid ozonide was treated with zinc dust (2 g.) and aqueous acetic acid (30 ml., 50%). Steam distillation of this mixture produced no volatile carbonyl compounds. The absence of nopinone at this point excludes an exocyclic double bond in I. The liquid remaining in the steam distillation flash was filtered, neutralized with sodium carbonate and extracted with ether. Evaporation of the ethereal solution gave a residue (2.65 g.) which reduced Tollen's reagent. The infrared spectrum of this material with bands at 3.70, 5.70, 5.76 and 5.81 μ confirmed the presence of aldehydo, keto and ester groups and thus establishes the position of the carbon-carbon double bond in I.

Saponification and Regeneration of Adduct I.—The adduct (17.5 g.) was heated for 1 hour under reflux with a solution of potassium hydroxide (5 g.) in aqueous ethanol (30 ml., 50%). Neutral components were removed by ether extraction, and the aqueous layer was carefully evaporated to dryness. This residue was twice recrystallized from ethyl acetate–ether to produce shiny platelets of a pure potassium salt (6.15 g.). The pure salt was dissolved in water (50 ml.) and neutralized with hydrochloric acid. The precipitated acid was filtered, dried under vacuum and esterified with diazomethane to produce a methyl ester, b.p. 88–90° (0.5 mm.), $n^{25}\text{D}$ 1.4818, $[\alpha]^{26}\text{D}$ −29.42°. The infrared spectrum of this material was indistinguishable from that of the original adduct.

Thermal Decomposition of Adduct I.—The adduct (1.19 g.) was dissolved in β-pinene (7 ml.) containing hydroquinone (2 mg.), and the solution was heated at 165° for 3 days. The clear solution was fractionated, and the portion boiling at 134–145° (760 mm.) collected. This fraction yielded a semicarbazone derivative (m.p. 191–192°) identical with that prepared from an authentic sample of methyl pyruvate.

Anal. Calcd. for $C_5H_9N_3O_3$: N, 26.41. Found: N, 26.35.

Methyl 2-Hydroxy-2-methyl-5-phenylpenten-4-oate (II).—A solution prepared from methyl pyruvate (25.5 g.), hydroquinone (0.1 g.) and allylbenzene (295 g.) was sealed in a Carius tube and heated at 190–200° for 48 hours. The excess allylbenzene, contaminated with methyl pyruvate, was removed under diminished pressure, and the residue was fractionated to give the α-hydroxy ester (12.1 g., 22%), b.p. 110–111° (0.4 mm.), $n^{25}\text{D}$ 1.5340.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.86; H, 7.62.

Methyl 2-Hydroxy-2-methyl-5-phenylpentanoate.—The adduct II (5.5 g.) dissolved in ethanol (25 ml.) was hydrogenated quantitatively over palladized charcoal (0.2 g.) at a hydrogen pressure of 40 lb./sq. in., b.p. 118° (0.7 mm.), $n^{25}\text{D}$ 1.5000.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.15.

Proof of Structure of Adduct II.—The position of the carbon–carbon double bond in II was established (a) by ozonization to benzoic acid and (b) by means of its ultraviolet absorption spectrum ($\lambda_{\text{max.}}$ 250 mμ, ε 17,200) which proves that the double bond in II is conjugated with the phenyl group.

The adduct II (4.4 g.) was converted into its dihydro derivative, and this product was reduced with lithium aluminum hydride to a 1,2-glycol. Oxidative cleavage of this material with lead tetraacetate, using the same conditions as employed in the determination of structure for adduct I, gave formaldehyde (identified by means of its 2,4-dinitrophenylhydrazone) and 5-phenyl-2-pentanone (2.4 g., over-all yield 75%), b.p. 92° (0.2 mm.), $n^{25}\text{D}$ 1.5070.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.36; H, 8.91.

The infrared spectrum, boiling point, refractive index and semicarbazone (m.p. 128°) of this ketone were identical with those obtained from an authentic sample of 5-phenyl-2-pentanone prepared by an independent synthesis.[11]

Pyrolysis of Adduct II.—The adduct II (10.5 g.) was dissolved in dry benzene (20 ml.), and this solution was added dropwise (over 30 min.) to a glass-helices packed column (diameter 20 mm., length 1′) maintained at 500°. Nitrogen was employed as an inert atmosphere and as sweep gas. Benzene was removed from the condensate by distillation, and the residue was fractionated through a spinning-band column to give (a) fraction 1 (0.3 g., b.p. 137–139° (760 mm.)) and (b) fraction 2 (3.2 g., b.p. 158–162° (760 mm.)). Fraction 1 was identified as methyl pyruvate. Fraction 2 was analyzed by means of its ultraviolet spectrum and by gas phase chromatography. It consisted of allylbenzene (77%) and propenylbenzene (23%); the latter being formed undoubtedly by isomerization of allylbenzene during the pyrolysis.[7]

Low Temperature Thermal Decomposition of Nopol (III).—A solution of pure nopol (0.83 g.), hydroquinone (2 mg.) and tetralin (10 ml.) was maintained under reflux (198°). During the entire heating period (24 hours) any volatile materials formed were swept out of the reaction flask with dry nitrogen and passed through a wash bottle containing 2,4-dinitrophenylhydrazine (1% in 4 *N* H_2SO_4). The yellow precipitate (0.116 g., 11%, m.p. 167°) so formed was collected and identified as formaldehyde 2,4-dinitrophenylhydrazone by comparison with an authentic sample. No decomposition of nopol could be observed in boiling xylene (b.p. 140°) during a 24-hour period.

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[11] I. M. Heilbron, R. N. Heslop, F. Irving and J. S. Wilson, *J. Chem. Soc.*, 1336 (1931).