Cyclization of 2-(4'-Carbomethoxy-2'-oxobutyl)-2-carbomethoxycyclohexanone[1a]

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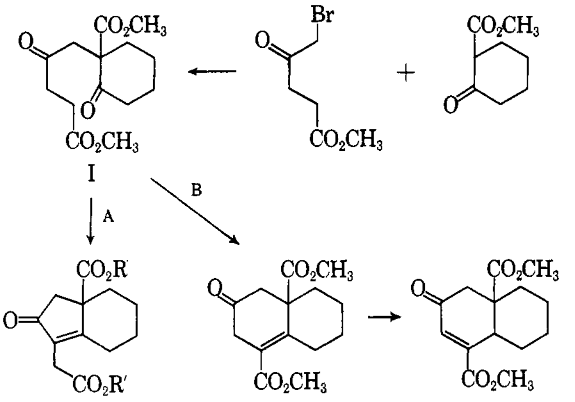
Systems like 2-(4'-carbomethoxy-2'-oxobutyl)-2-carbomethoxycyclohexanone (I) can in principle undergo intramolecular aldol cyclization involving either the C-3' (α to the ketone, path A) or the C-4' (α to the ester, path B) methylene group. Since enolages are normally more readily generated from ketones than from esters one might well expect the former course, leading to the 2-hydrindenone derivative II, to be favored in a rate-controlled process. However, the β,γ-unsaturated keto diester III from path B could be converted into its α,β-unsaturated isomer IV under basic reaction conditions, and it seemed possible that reversibility of the various steps involved might allow equilibrium control of the product and thus lead to IV with its more conjugated system and less strained ring. In order to determine which course was in fact followed, we examined this cyclization.



IIa, R = R' = CH_3
b, R = CH; R' = H
c, R = CH_3; R'CH

Alkylation of 2-carbomethoxycyclohexanone by methyl 5-bromolevulate[2] using sodium hydride in benzene[3] readily afforded the diketo diester I at room temperature, although subsequent aldol cyclization proceeded to a considerable extent at elevated temperatures. Treatment of this diketo diester with potassium *t*-butoxide in *t*-butyl alcohol–benzene gave an acidic product in 70% yield, and on esterification with diazomethane this produced a single keto diester. That this product was not III was evident from the intense ultraviolet absorption which both it and its acidic precursor possessed at 237 mμ (unchanged in base), a wave length which was incompatible with the presence of only the octahydronaphthalenic α,β-unsaturated ester or acid chromophore,[4] and from its behavior in the deuterium exchange experiments described subsequently. That it was not IV was indicated by absence of vinyl proton resonance from its n.m.r. spectrum. On the other hand, all of these properties are in accord with the 2-hydrindenone structure IIa,[5] as are the remaining features of the n.m.r. spectrum (two methoxyl resonances at 6.25 and 6.28 τ, a slightly broadened two-proton singlet at 6.70 τ from methylene between olefinic and carbonyl carbon, and an AB quartet with τ_A = 7.32, τ_B = 7.67, and J_{AB} = 19 c.p.s. from the C-1 methylene flanked by a carbonyl group and a quaternary center), and the infrared spectrum. No other reasonable isomeric structure which might arise from the diketo diester I upon base treatment adequately encompasses all these observations.[6] Thus at least under these conditions path B does not compete favorably with path A.

The direct product of the cyclization was an acid rather than the keto diester IIa, and this may afford some insight into the sequence of steps involved. Initial attack of the enolate on the cyclohexanone carbonyl produces the ketolate ion VI. In this structure the alkoxide is β to the angular ester and γ to that on the side chain, and thus either of two lactonic intermediates, V or VII, could intervene in the elimination step. Such γ-lactonization is, of course, the common event in the Stobbe reaction[7] and related processes, while β-lactone intermediates, although less common, have probably also been encountered, indeed in systems quite similar to this one.[8] A decision between these courses is clearly possible in the present instance,

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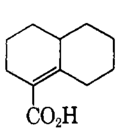
[1] (a) Abstracted in part from the M.S. thesis of Barbara S. Bielaski, Indiana University, 1963; (b) Indiana University Graduate School Fellow, 1961–1962; (c) contribution number 1147.

[2] Modifications of the method of C. Rappe, *Arkiv. Kemi*, **14**, 467 (1959), for preparation of the bromoketone are described in the Experimental section. Compare A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820 (1954), and V. M. Rodinov and M. A. Gubareva, *Zh. Obshch. Khim.*, **23**, 1830 (1953).

[3] J. Hartman, *J. Org. Chem.*, **22**, 466 (1957).

[4] *Cf.* A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957), and references cited therein. Systems i and ii contain the chromophore of III, and are reported to absorb at 219 and 225 mμ, respectively. It seems highly unlikely that homoallylic interaction with the ketone and/or angular ester functions of III would produce a shift as large as 18 mμ, especially since the angular ester has little or no effect on the hydrindenone system (ref. 3).



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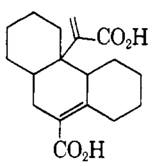

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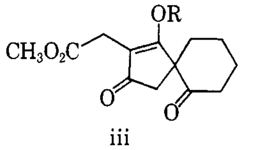
[5] For example, 1-methyl-$\Delta^{1,8}$-2-hydrindenone and its 9-carbethoxy derivative both absorb at 239 mμ (ϵ 18,150 and 13,940, respectively) (ref. 3).

[6] Derivation of these products is an amusing exercise in carbonyl chemistry. For example, β-dicarbonyl derivatives such as iii or iv (R = H) could arise through condensation of the side chain with the quaternary ester rather than the cyclohexanone carbonyl. In addition to being more difficult to reconcile with the spectral data, however, such compounds should undergo a color reaction with ferric chloride, their ultraviolet spectra should change on treatment with base, and both the acids and the methyl ethers (R = CH_3) should exchange two more α-hydrogens (on the cyclohexanone ring) than do the observed products, etc.



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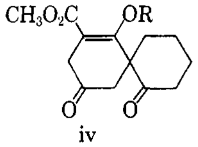
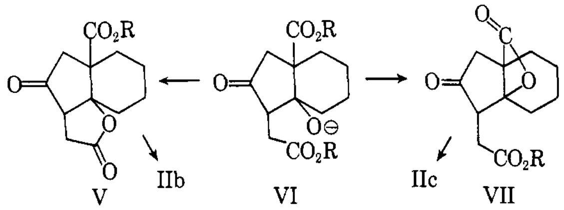


iv

[7] W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

[8] W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961); G. Stork and F. H. Clarke, *J. Am. Chem. Soc.*, **83**, 3114 (1961); W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, **27**, 3263 (1962).

for if it is the γ-lactone V which is formed and undergoes elimination, the *side-chain* carboxyl of II should be the free acid (IIb), while in the case of β-lactone (VII) intervention the *angular* group should be the carboxyl (IIc). That the acidic product was indeed one of these half esters was clear from its n.m.r. spectrum, which was nearly superimposable on that of the diester except that it contained only *one* methoxyl resonance (6.25 τ). Both the C-1 methylene AB quartet and the side-chain methylene singlet were absent from the spectrum of diester in which the four α-hydrogens had been exchanged for deuterium by treatment with sodium methoxide in methanol-*d*. Under identical conditions (which thus should replace all four α-hydrogens in IIc) only two hydrogens were lost from the half ester, and only the AB quartet disappeared from the spectrum. Thus the half ester must be IIb, exchange at the side-chain methylene being inhibited by the adjacent carboxylate ion, and if a lactone is involved in the aldol cyclization–elimination sequence it must be the γ-lactone V. An alternate mechanism in which the less hindered side-chain ester is preferentially saponified by potassium hydroxide formed through elimination of water from the ketol is not, of course, excluded by this evidence.



Experimental[9]

Methyl 5-Bromolevulate.—β-Carbomethoxypropionyl chloride was treated with ethereal diazomethane by the procedure of Rappe,[2] save that the time for this reaction was shortened to 4 hr., and the diazoketone was decomposed by passing dry hydrogen bromide through the mixture at ice–salt temperature until nitrogen evolution ceased and the mixture was colorless. The mixture was washed with saturated sodium chloride and sodium bicarbonate solutions, dried, and the product isolated by distillation to afford 83% of the bromo ketone, b.p. 83.5° (0.8 mm., bath temp., 95°) [reported[2] b.p. 125–128° (9 mm.)].

2-(4′-Carbomethoxy-2′-oxobutyl)-2-carbomethoxycyclohexanone (I).—A suspension of 2.10 g. of a 53.7% dispersion of sodium hydride in mineral oil (Metal Hydrides, Inc.) in 40 ml. of dry benzene under a dry nitrogen atmosphere was washed four times with 40-ml. portions of benzene to remove mineral oil. The sodium hydride was suspended in 50 ml. of benzene and 7.50 g. of 2-carbomethoxycyclohexanone, b.p. 76° (4 mm.), was added slowly with stirring.[3] After gas evolution ceased the mixture was cooled to 10°, 10.0 g. of methyl 5-bromolevulate, b.p. 83.5° (0.8 mm.), was added dropwise to the white pasty sodium salt, and the mixture was stirred at room temperature for 25 hr. An equal volume of water was added, the mixture was acidified with hydrochloric acid, and the product was isolated by separation of the phases, extraction with ether, washing with 5% sodium bicarbonate, drying, and evaporation of the solvent. Distillation afforded 4.0 g. (54%) of starting β-keto ester, b.p. 42° (0.01 mm.), and then 6.0 g. (44%) of the diketo diester I, b.p. 152–158° (0.01 mm.); λ_{max}^{film} 5.74, 5.83 μ. Considerable decomposition occurred in the still pot during distillation, a difficulty which was apparently responsible for our failure to obtain a sample which gave satisfying elemental composition results, although vapor phase chromatography of once-distilled product showed but one peak. Redistillation at 0.3 mm. in a microapparatus, bath temperature 100°, gave a sample with $n^{20}D$ 1.4802.

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found:[10] C, 58.55; H, 6.7.

A very insoluble bissemicarbazone was prepared in the usual manner.[11] No suitable solvent was found for its recrystallization, so it was washed several times alternately with water and warm methanol to afford material with m.p. 198° dec.

Anal. Calcd. for $C_{16}H_{26}N_6O_6$: C, 48.23; H, 6.58; N, 21.09. Found:[10] C, 48.5; H, 6.9; N, 21.0.

Cyclization of Diketo Diester I.—To a solution of 310 mg. of potassium in 15 ml. of dry *t*-butyl alcohol was added 2.0 g. of redistilled diketo diester I (95% pure by v.p.c.) in 15 ml. of benzene. The mixture was allowed to stand for 23 hr. at room temperature in an atmosphere of nitrogen, and then an equal volume of cold saturated sodium chloride solution was added and the mixture was acidified to congo red paper with hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with sodium bicarbonate solution, dried, and evaporated to dryness, leaving 0.34 g. (17%) of a yellow oil, mainly starting material according to v.p.c. analysis.

The bicarbonate washings were acidified with hydrochloric acid and the precipitate was isolated by ether extraction to afford 1.24 g. (71%) of half-ester IIb as a pale yellow solid, m.p. 122.5–123° (gas evolution), which gave no color reaction with ethanolic ferric chloride; λ_{max}^{KBr} 3.0–4.0, 5.78, 5.87, 6.03 μ; $\lambda_{max}^{95\%\ EtOH}$ 237 mμ, unaltered in the presence of sodium hydroxide; n.m.r. ($CDCl_3$), 6.25 τ.

Treatment of the crude half-ester IIb with excess ethereal diazomethane followed by evaporation of the ether afforded a yellow oil which according to v.p.c. analysis consisted of 95% of one substance. Distillation at 0.1 mm. with a bath temperature of 105° gave the keto diester IIa as a colorless oil, $\lambda_{max}^{95\%\ EtOH}$ 237.5 mμ (ε 21,700), 302 mμ(117); λ_{max}^{film} 5.75, 5.82, 6.02 μ; n.m.r. ($CDCl_3$), 6.28 (s), 6.25 τ (s).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found[12]: C, 62.9; H, 6.9.

A semicarbazone was prepared and recrystallized from methanol to m.p. 184–185° dec.

Anal. Calcd. for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found[10]: C, 56.0; H, 6.6; N, 13.0.

Deuterium Exchange Experiments.—To 2.0 ml. of an 0.8% solution of sodium methoxide in methanol-*d* (prepared by twice equilibrating one volume of absolute methanol and 2.5 volumes of 99% deuterium oxide, followed by distillation and redistillation from magnesium oxide) was added 90 mg. of diester IIa or 55 mg. of half-ester IIb, and the mixture was held at 65–70° for 1 hr. and then at room temperature overnight. The product was isolated by acidification and ether extraction after addition of water, and its n.m.r. spectrum was examined. The spectrum of recovered diester was identical with that of starting material except peaks at 198, 174, 155, 146, and 127 c.p.s. from internal tetramethylsilane, equivalent to four protons, were missing. The spectrum of recovered half ester was identical with that of starting material except peaks at 174, 155, 146, and 127 c.p.s., equivalent to two protons, were missing.

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(9) N.m.r. spectra were obtained from dilute solutions using a Varian Associates A-60 spectrometer, infrared spectra were obtained on Perkin-Elmer Models 137 and 137G spectrophotometers, and ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer. Melting points are uncorrected.

(10) Microanalysis by Alfred Bernhardt, Mulheim, Germany.

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 218.

(12) Microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich.