Studies in Steroid Total Synthesis. VI. Exploration of an Alternate Route to *anti-trans* - 2,3,4,4a,4b,5,8,8a - Octahydro - 8a-methyl-2-oxophenanthrene-1-propionic Acid

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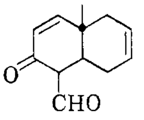
The tricyclic keto acid (−) *anti-trans*-2,3,4,4a,-4b,5,8,8a - octahydro - 8a - methyl - 2 - oxophenanthrene-1-propionic acid (IIIa), prepared in two steps from I and methyl 5-oxo-6-heptenoate (II), proved to be a key intermediate in a stereoselective ring A synthesis recently reported from this laboratory.[1] Early preparations of the vinyl ketone II were characterized by low yields and poor quality which complicated the synthesis of IIIa in quantity. These difficulties were eventually overcome, but the exploration of an alternative route to IIIa seemed advisable at the time. Some results of this investigation are reported herein. A good route to the unsubstituted tricyclic ketone IIIb was found, but the desired alternative synthesis of IIIa was realized only in a formal sense.

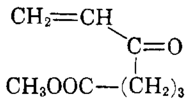
Treatment of I with aqueous alkali and formaldehyde gave a good yield of a mixture of bicyclic methylene (IV) and methylol (V) ketones. Condensation of IV with dihydroresorcinol using potassium *tert*-butoxide as catalyst gave a 63% yield of the adduct VIa. Hydrolytic cleavage of VIa at one of the indicated points followed by cyclization of the resulting open chain keto acid would be expected to yield IIIa directly. Unfortunately, in agreement with the observations of Wilds *et. al.*,[2] 2-monosubstituted 1,3-cyclohexanediones are quite enolic, and thus, are resistant to hydrolytic cleavage. In our case, only prolonged alkaline hydrolysis was sufficient to cleave VIa. The maximum yield from VIa to IIIa was roughly 35%. Isolation of IIIa was complicated by its poor crystallizing properties. A major side reaction to ring opening appeared to be a reverse Michael reaction[3] resulting in a large oily neutral fraction presumably derived from IV by a self-condensation. That the resistance of the 1,3-cyclohexanedione moiety of IVa to hydrolytic cleavage was due solely to its enol character was shown by the fact that conversion to VIb gave a product cleaved readily by dilute alkali.

The material resulting from this 1,3-diketone cleavage and subsequent cyclization was an impure, somewhat unstable noncrystalline keto acid whose gross structure appeared to be VIIa. Conversion to the methyl ester and purification on alumina gave an oily ester ($\lambda_{\max}^{\text{alc}}$ 292 mμ, ε 17,000) in excellent agreement with the ultraviolet spectrum ($\lambda_{\max}^{\text{alc}}$ 292 mμ, ε 19,800) for the thiophenyl substituted dienone chromophore VIII previously observed in connection with another study.[4] Several attempts to desulfurize VIIa to IIIa were attended by considerable reduction of the dienone system, and eventually this approach was abandoned.

In contrast to the difficulties in the preparation of IIIa, the unsubstituted tricyclic ketone (−) *anti* - *trans* - 4,4a,4b,5,8,8a - hexahydro - 8a-methyl-2(3*H*) phenanthrone (IIIb) was obtained smoothly and in good yield by condensation of IV with ethyl acetoacetate under the influence of a catalytic amount of potassium *tert*-butoxide. Ring closure and loss of water occurred immediately subsequent to addition of the keto ester to IV. The intermediate 3-carbethoxy ketone IIIc was hydrolyzed and decarboxylated to IIIb without isolation. Presumably ketones similar to IIIb where R = alkyl could also be prepared using β-keto esters more complex than acetoacetic ester.

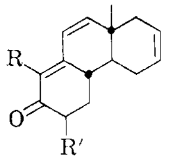


I



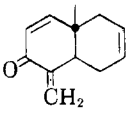
$$\begin{array}{l} CH_2{=}CH \\ \quad\quad\;\; \diagdown C{=}O \\ \quad\quad\quad\;\, | \\ CH_3OOC{-}(CH_2)_3 \end{array}$$

II

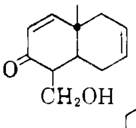


III

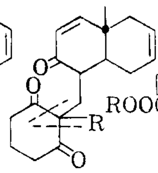
a. R = CH_2CH_2COOH, R′ = H
b. R = H, R′ = H
c. R = H, R′ = COOEt



IV

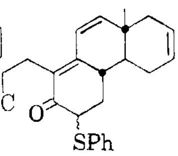


V



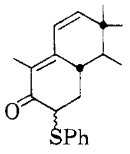
VI

a. R = H
b. R = SPh



VII

a. R = H
b. R = CH_3



VIII

EXPERIMENTAL

(−) *trans-4a,5,8,8a-Tetrahydro-4a-methyl-1-methylene-2(1H) naphthalenone* (IV) *and* (−) *trans-4a,5,8,8a-tetrahydro-4a-methyl-1-methylol-2(1H) naphthalenone* (V). To 19

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[1] L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).

[2] A. L. Wilds, J. Ralls, W. D. Wildman and K. E. McCaleb, *J. Am. Chem. Soc.*, **72**, 5794 (1950). See also Wilds, *et al.*, U. S. Patent **2,674,627**.

[3] For a discussion of the inverse Michael reaction see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y., 1953; p. 695. *Cf.* also C. A. Grobe and W. Bauman, *Helv. Chim. Acta*, **38**, 595 (1955); S. A. Julia, A. Eschenmoser, H. Heusser, and N. Tarkoy, *Helv. Chim. Acta*, **36**, 1885 (1953); M. N. Tilichenko, *J. Gen. Chem. U.S.S.R.*, **25**, 2503 (1955) for other recent examples.

[4] W. S. Knowles and Q. E. Thompson, *J. Am. Chem. Soc.*, **79**, 3212 (1957).

g. of the formyl ketone[5] I in 110 ml. of water plus 40 ml. of 36% aqueous formaldehyde at 5° was added over 2 hr. a solution of 4.5 g. of sodium hydroxide in 40 ml. of water. Vigorous agitation was maintained through the reaction period and for an additional 2 hr. Ether (150 ml.) was then added and the layers were separated. The aqueous layer was extracted once with 80 ml. of ether and discarded. The ether layers were combined, washed once with 50 ml. of water, and dried with "Drierite." Removal of solvent gave 16.5 g. of a clear, pale yellow oil which was subjected to vacuum distillation. Two fractions of distillate were collected 5.9 g., b.p. 119–123° (4 mm.) and 3.3 g., b.p. 124–145° (4 mm.). About 300 mg., the center portion of the first cut, was collected for analytical purposes. This material was good quality methylene compound IV, $\lambda_{\max}^{\text{alc}}$ 238 mμ, ε 8,500; $[\alpha]_D^{25}$ −287° (2% chloroform), as a clear mobile liquid when freshly distilled. Standing for several days, even at 0°, caused appreciable polymerization.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.73; H, 8.10. Found: C, 82.06; H, 7.83.

The pot residue crystallized on cooling. The crude brown material was dissolved in 200 ml. of ether and decolorized by filtering through a column of activated carbon (5 g.). The clear liquor resulting was concentrated to about 20 ml., cooled, and seeded. The first crop of crystalline methylol compound V amounted to 3.5 g., m.p. 76–77°. Recrystallization once from ether–petroleum ether gave pure material, m.p. 77–78°, $[\alpha]_D^{25}$ −272° (2% chloroform).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39. Found: C, 74.71; H, 8.57.

(−) *trans-1(2,6-Dioxocyclohexylmethyl)-4a,5,8,8a-tetrahydro-4a-methyl-2(1H)naphthalenone* (VIa). To a solution of 5.93 g. of IV in 50 ml. of *tert*-butyl alcohol was added 4.0 g. of dihydroresorcinol[6] and 3.5 ml. of 1 molar potassium *tert*-butoxide solution. The mixture was held at 55° for 16 hr. under nitrogen. The excess alcohol was removed *in vacuo* and the residue treated with 80 ml. of 0.5 molar sodium hydroxide solution. The alkaline solution was extracted once with 100 ml. of ether and the ether extract discarded. After acidifying with concentrated hydrochloric acid, the oil liberated was taken up in two 100-ml. portions of ether. The ether extracts were washed once with water, dried with "Drierite," and the solvent removed. The residual oil (8.0 g.) crystallized almost completely on cooling and trituration with ether. The first crop of crystals collected amounted to 5.0 g., m.p. 113–115°, with a second crop of 1.12 g., m.p. 100–108°, total yield of crystalline material, 63%. Recrystallization of first crop material twice from hexane gave pure VIa, m.p. 115–116°; $[\alpha]_D^{25}$ −20.6°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.75. Found: C, 75.90; H, 7.75.

This adduct was also prepared though in somewhat lower yield (40–50%) using the purified methylol compound V or crude mixtures of IV and V. In these cases, the amount of potassium *tert*-butoxide was increased to a slight excess over the molecular equivalents of methylol present.

(−) *Anti-trans-2,3,4,4a,4b,5,8,8a-octahydro-8a-methyl-2-oxophenanthrene-1-propionic acid* (IIIa). Approximately 286 mg. of adduct VIa was refluxed under nitrogen for 24 hr. with 10 ml. of 0.5 molar sodium hydroxide solution. The reaction mixture was then cooled, 10 ml. of water was added, and the solution extracted once with 30 ml. of ether. The ether extract was set aside and the aqueous phase acidified with concentrated hydrochloric acid. The oily keto acid liberated was taken up by extraction with two 30-ml. portions of ether which were combined, washed with water, and dried. Removal of solvent left 162 mg. of oily keto acid IIIa, as evidenced by its infrared spectrum. The crude oil showed an ultraviolet absorption maximum of $\lambda_{\max}^{\text{alc}}$ 289 mμ, ε 17,000 as compared to the known maximum of $\lambda_{\max}^{\text{alc}}$ 289 mμ, ε 24,900 for pure IIIa. On the basis of this assay, the over-all yield of IIIa was 38%.

Isolation of pure crystalline IIIa from this crude product was accomplished by chromatography on alumina deactivated with water (15%). About 75 mg. of crystalline acid, m.p. 98–101°, was obtained by elution of the column with wet benzene and ether. Infrared and ultraviolet absorption spectra of this material indicated its identity with IIIa prepared by our alternate route.[1] In addition, a mixed melting point of 98–101° further established this fact.

trans-1(1-Phenylthio-2,6-dioxocyclohexylmethyl)-4a,5,8,8a-tetrahydro-4a-methyl-2(1H) naphthalenone (VIb). A suspension of 4.0 milliequivalents of potassium *tert*-butoxide in anhydrous toluene was prepared by distilling out excess *tert*-butyl alcohol from a mixture of 4.3 ml. of 0.95 molar potassium *tert*-butoxide solution and about 100 ml. of boiling anhydrous toluene. To this hot suspension was added 1.0 g. of the adduct VIa which was immediately converted to its insoluble potassium salt. Distillation was then continued until all of the alcohol had been removed. The yellow suspension was cooled to 10° and treated with 580 mg. of benzenesulfenyl chloride.[7] Reaction occurred almost immediately, and the heavy precipitate was replaced by a fine precipitate of potassium chloride. After stirring at room temperature for an hour, dilute hydrochloric acid and a little benzene were added. The water layer was separated, extracted with benzene, and discarded. The organic layer was washed once with water and the solvent was removed. The residual light brown oil amounting to 1.64 g. crystallized readily on trituration with ether. The first crop amounted to 520 mg., m.p. 161–164°, and chromatography of the residues on alumina gave another 100 mg. of product of similar quality. Several recrystallizations from benzene and ether gave pure material, m.p. 168–169°; $\lambda_{\max}^{\text{alc}}$ 231 mμ, ε 19,300.

Anal. Calcd. for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.63; S, 8.13. Found: C, 72.80; H, 6.80; S, 8.50.

Alkaline cleavage of VIb. A mixture of 400 mg. of VIb and 200 mg. of sodium acetate in 5 ml. of water and 10 ml. of methanol was treated at reflux with 2 ml. of 0.50 molar sodium hydroxide solution. The solid (VIb) began to dissolve slowly. After 4 hr., the yellow solution was cooled, water (50 ml.) and a little more base was added. The aqueous layer was extracted once with chloroform and the extract discarded. The acidic material in the aqueous phase was liberated by acidification with concentrated hydrochloric acid. A yellow oily acid separated. This was taken up in ether and washed. The solution was dried with "Drierite" and the solvent removed leaving 248 mg. of yellow glass. The acid was converted immediately to its methyl ester with diazomethane and the latter cleaned up by passing over a short column of alumina. The clear yellow oily ester showed absorption in the ultraviolet at $\lambda_{\max}^{\text{alc}}$ 292 mμ, ε 17,000. Although the infrared spectrum of the purified ester or the free acid derived from it by hydrolysis was that expected for VIIb and VIIa, respectively; no crystalline material could be obtained.

(−) *Anti-trans-4,4a,4b,5,8,8a-hexahydro-8a-methyl-2(3H)-phenanthrone* (IIIb). To a solution of 1.087 g. of freshly distilled methylene ketone IV in 20 ml. of *tert*-butyl alcohol was added 1.04 g. of ethyl acetoacetate and 2 ml. of 1 molar potassium *tert*-butoxide solution. The pale yellow solution was allowed to stand at room temperature under nitrogen for 48 hr. About 20 ml. of water was then added and most of the alcohol and water were slowly distilled out. Ethanol (20 ml.) and 20 ml. of 0.5 molar sodium hydroxide were added and alcohol and water again distilled out until the volume was reduced to about 15 ml. This residue was treated with 4 ml. of 6 molar hydrochloric acid and refluxed for 30 min. The mixture was cooled and treated with 20 ml. of water and 50 ml. ether. After separating the layers,

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(5) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5014 (1954).

(6) R. B. Thompson, *Org. Syntheses*, **27**, 21 (1947).

(7) H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

the water phase was extracted once with ether and discarded. The ether layers were combined, washed with a little water, and dried with "Drierite." The solvent was removed leaving 1.20 g. (90%) of a clear, yellow oil which solidified completely when touched with a spatula, m.p. 97–98°. The crude material was recrystallized twice from hexane to obtain the analytical sample, m.p. 102.5–103.5°; λ_{max}^{alc} 281 mμ, ε 25,000; $[\alpha]_D^{25}$ −480° (2% chloroform). The infrared spectrum of this optically active ketone was identical with that of the racemic material first prepared by Woodward, *et al.*[8]

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.46. Found: C, 84.24; H, 8.74.

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(8) See footnote number 25 of the paper by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

Ozonization of Cycloöctatetraene

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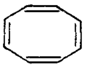
Previous ozonizations of cycloöctatetraene in non-hydroxylic solvents led to the conclusion that it reacts with ozone through the fused ring structure II.[2] Although no physical evidence indicated the presence of this structure in equilibrium with cycloöctatetraene I, studies in bromination of I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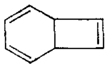
II

have demonstrated that certain cationic additions may proceed through this form.[3–5] Furthermore, rearrangement reactions[6] of cycloöctatetraene have been considered as typical homoallylic rearrangements[7] and for this reason ozonization reactions of this cycloölefin, under certain conditions, may be expected to proceed abnormally. It is therefore possible that the extremely low yields (1 to 2%) of the ozonization products reported by Wibaut and Sixma may have been due to abnormal rearrangements and the conclusions drawn may not be entirely valid.

Since we have already shown that abnormal ozonizations of allylic compounds proceed normally in hydroxylic solvents[8] to give high yields of normal products, we felt that the ozonization of cyclooctatetraene in these solvents may give results in accordance with its normal structure.

Accordingly, therefore, freshly purified cycloöctatetraene[9] was ozonized in methanol under various conditions and the peroxide intermediate formed in each case reduced with sodium bisulfite and immediately the 2,4-dinitrophenylhydrazone precipitated. The results of three independent experiments are recorded in Table I.

TABLE I

OZONIZATION OF CYCLOÖCTATETRAENE

Temp., °C.	C.O.T., Mmoles	O_3 Added, Mmoles	O_2 Absorbed, Mmoles	Active (O), M Atoms	Glyoxal, Mmoles
−16.5	10.03	42.7	40.6	25.6	15.0
−20	10.00	80.0	—	49.0	22.0
−78	5.22	44.1	23.7	17.9	20.0

The rate with which cycloöctatetraene absorbed the first three moles of ozone was fairly constant, then the rate decreased and much of the ozone passed through unabsorbed during the addition of the last mole. Consequently the solution in the last two cases was overozonized purposely in order to insure complete reaction.

At the end of each experiment and after the dissolved ozone was removed by passing through the mixture dry nitrogen, the peroxide content of the solution was determined and the total active oxygen recorded in Table I, column five. At −20° the peroxide found was much more than the amount expected and the excess was attributed to methyl hydroperoxide and other peroxides[10] which form from methanol after the olefin is completely consumed. At −20° methanol absorbs ozone at the rate of 7.8 mmoles per hr. while at −78° the rate is negligible. However, the formation of peroxides from methanol does not affect our results since reduction of the pure ozonized methanol with aqueous sodium bisulfite gave no carbonyl compounds.

Finally, the results shown in Table I indicate that, under the conditions of our experiments, cycloöctatetraene ozonizes in accordance with structure I rather than II as previously proposed.

EXPERIMENTAL

In 80 cc. of methanol was dissolved 1.042 g. (0.01 mole) of freshly distilled cycloöctatetraene and the solution cooled to −20°. Ozone was then passed through the solution for two hr. at the rate of 0.04 mole per hr. Dry nitrogen was

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(1) From the Ph.D. Thesis of John T. Nolan, Jr., Massachusetts Institute of Technology, May, 1955.

(2) J. P. Wibaut and F. L. J. Sixma, *Rec. trav. chim.*, **73**, 797 (1954).

(3) S. L. Friess and V. Boekelheide, *J. Am. Chem. Soc.*, **71**, 4145 (1949).

(4) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948).

(5) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(6) A. C. Cope, N. A. Nelson, and D. S. Smith, *J. Am. Chem. Soc.*, **76**, 1100 (1954).

(7) E. Vogel, Habilitationshrift, Karlsruhe, 1957.

(8) N. A. Milas and J. T. Nolan, Jr., Paper presented before the International Ozone Conference, Chicago, November 1956.

(9) We are indebted to Prof. A. C. Cope for the cyclooctatetraene used in this work.

(10) The structure of these peroxides is being investigated.