Medium-Ring 3-Carboxycycloalkanones. Synthesis and Keto–Enol Equilibria

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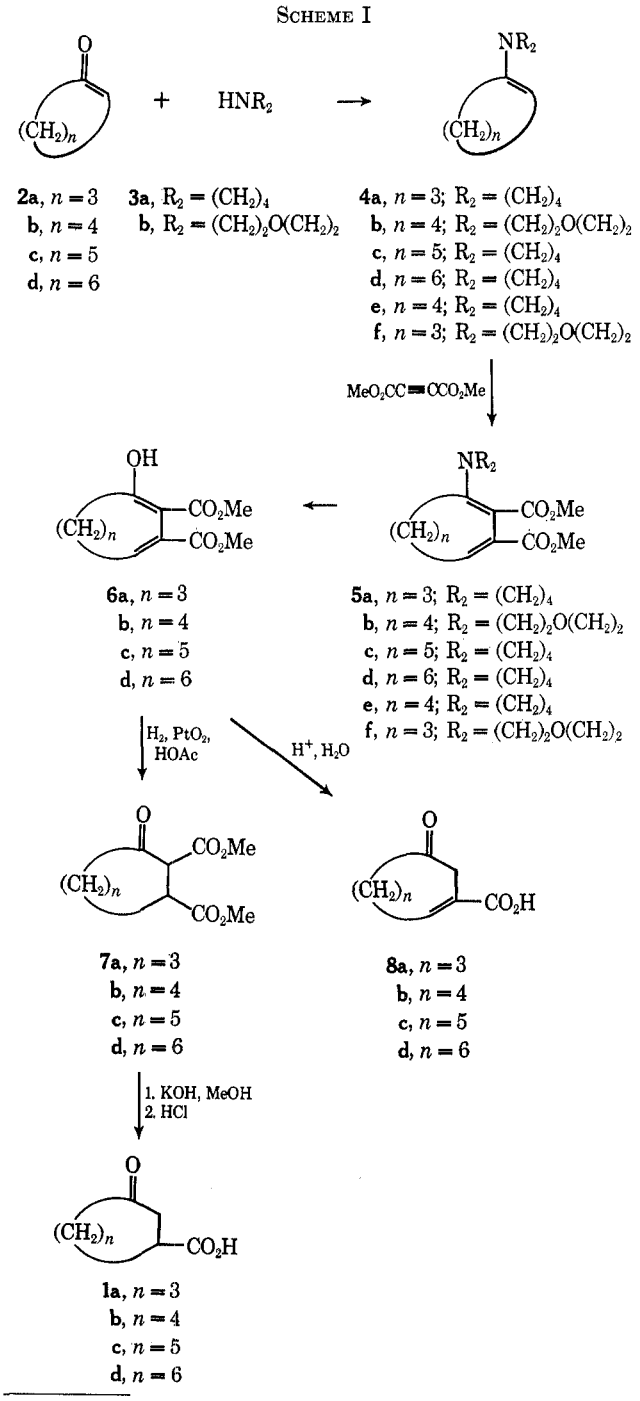
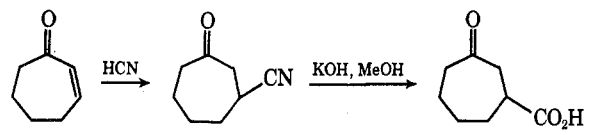
The title compounds with ring sizes seven to ten were prepared by several synthetic routes, exposing instances of reactivity extremely sensitive to ring size. Trends in enol content of the 3-carboxycycloalkanones and various unsaturated and 2,3-dicarboxycycloalkanone precursors are evaluated.

The 3-carboxycycloalkanones (**1a–d**) provide attractive synthetic precursors for a variety of medium-sized ring systems. Berchtold and Uhlig[2] have reported the preparation of 3-carboxycycloheptanone (**1a**) by two routes. The first route (Scheme I) was lengthier, but involved more readily available starting materials. The pyrrolidino or morpholino enamines of cyclopentanone (**4a** or **4f**) were treated with dimethyl acetylenedicarboxylate to effect expansion of the carbocyclic ring by two carbon atoms.[2–5] The resulting adducts, **5a** and **5f**, were hydrolyzed to dimethyl 7-hydroxy-2,7-cycloheptadiene-1,2-dicarboxylate (**6a**). Catalytic reduction with prereduced platinum oxide in glacial acetic acid to the saturated keto dicarboxylic ester **7a** was followed by saponification and acidic monodecarboxylation to 3-carboxycycloheptanone (**1a**). Alternatively, Berchtold and Uhlig[2] prepared the 3-carboxycycloheptanone by hydrolysis of 3-cyanocycloheptanone, the result of a Michael addition of hydrogen cyanide to 2-cycloheptenone. The products from the two routes exhibited identical infrared spectra.[2]

SCHEME I





1a

The ring-expanded enamines **5a–e** were prepared by the methods of Berchtold and Uhlig[2] and Paquette and Begland.[6] The morpholino enamine in the eight-membered ring system, **5b**, was used instead of the corresponding pyrrolidino enamine because of poor yields in the ring expansion of the 1-*N*-(pyrrolidino)cyclohexenone (**4e**). Hydrolysis with acidic methanol[2,6] produced good yields of the crystalline seven-, eight-, and ten-membered unsaturated keto dicarboxylic esters **6a**, **6b**, and **6d**. The first two compounds were essentially 100% enolic, while the ten-membered ring compound[7] after 2 days at room temperature was found to be 53% enolic in a 10% solution in deuteriochloroform and 65% enolic in a 10% solution in carbon tetrachloride (by integration of the proton magnetic resonance spectra).[8] The oily material obtained by Paquette and Begland[6] corresponding to **6d** exhibited 41% and 57% enol in deuteriochloroform and carbon tetrachloride, respectively. The nine-membered ring compound **6c** was obtained only as an oil in poor yield. The spectral characteristics of this compound agree with those of Paquette,[6]

(1) Author to whom correspondence should be directed.

(2) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).

(3) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963).

(4) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28**, 3134 (1963).

(5) A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Lett.*, 1467 (1963).

(6) L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **88**, 4685 (1966).

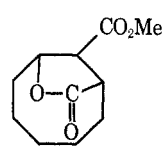
(7) Recrystallization of this ten-membered unsaturated keto diester **6d** from varying proportions of methanol and water produced isomeric material with slightly different physical properties and slightly different behavior toward thin layer chromatography. See the Experimental Section for details.

(8) Enol content refers to [enol]/[keto] ratios calculated from integrated nmr signal intensities unless otherwise noted. See Table I.

but the compound was shown to be impure by elemental analysis even after repeated attempts at purification. The major product from this reaction mixture was identified as 8-oxo-1-cyclononenecarboxylic acid (**8c**) (*vide infra*).

Catalytic reduction of dimethyl 7-hydroxy-2,7-cycloheptadiene-1,2-dicarboxylate (**6a**) by the method of Berchtold[2] proceeded with difficulty to give impure saturated **7a**, which was the major component when hydrogen absorption effectively ceased, but which we could not purify. Increased hydrogenation pressures[9] or a change to 5% palladium on carbon in ethanol at 40 psig[10] did not improve the results. When various purification procedures failed, the crude **7a** was subjected to the Berchtold–Uhlig saponification–decarboxylation sequence.[2] A low yield of a mixture containing at least four components was produced. Because of the possibility of ring opening under the alkaline conditions,[11] the conversion of **7a** to **1a** was attempted under acidic conditions. The infrared and proton magnetic resonance spectra of the crude reaction product suggested the presence of starting material and a lactone, but little of the desired keto carboxylic acid.

Catalytic hydrogenation of dimethyl 8-hydroxy-2,8-cyclooctadiene-1,2-dicarboxylate (**6b**) with prereduced platinum oxide in glacial acetic acid at 40 psig proceeded in a somewhat more satisfactory fashion than with the lower homolog **6a**. Hydrogen absorption did not show a reproducible inflection point or cease at the equimolar ratio, the products after 100, 120, or 200% hydrogen absorption being dimethyl 8-oxocyclooctane-1,2-dicarboxylate (**7b**), unreacted starting material, and lactonic material. Fractional distillation followed by column chromatography on silica gel effected separation of the saturated keto dicarboxylate ester **7b**, starting material, and a lactone identified as **9**. Acidic hydrolysis and decarboxylation of **7b** produced pure 3-carboxycyclooctanone (**1b**).



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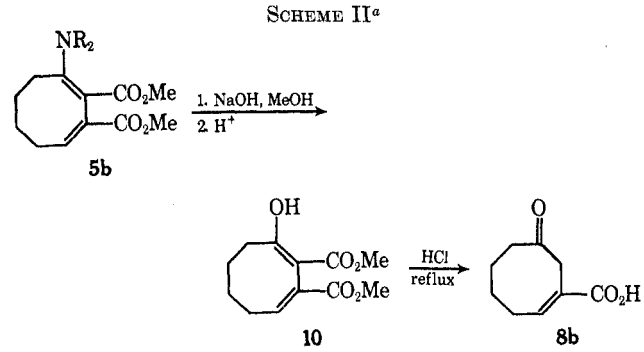
Catalytic hydrogenation of the unsaturated ten-membered ring compound **6d** was performed as for the lower homolog **6b**. The hydrogenation stopped at 93.5% of theoretical hydrogen absorption to give a good yield of the desired dimethyl 10-oxocyclodecane-1,2-dicarboxylate (**7d**) with a slight lactonic contaminant. Purified **7d** was hydrolyzed and decarboxylated under acidic conditions to produce good yields of pure 3-carboxycyclodecanone (**1d**).

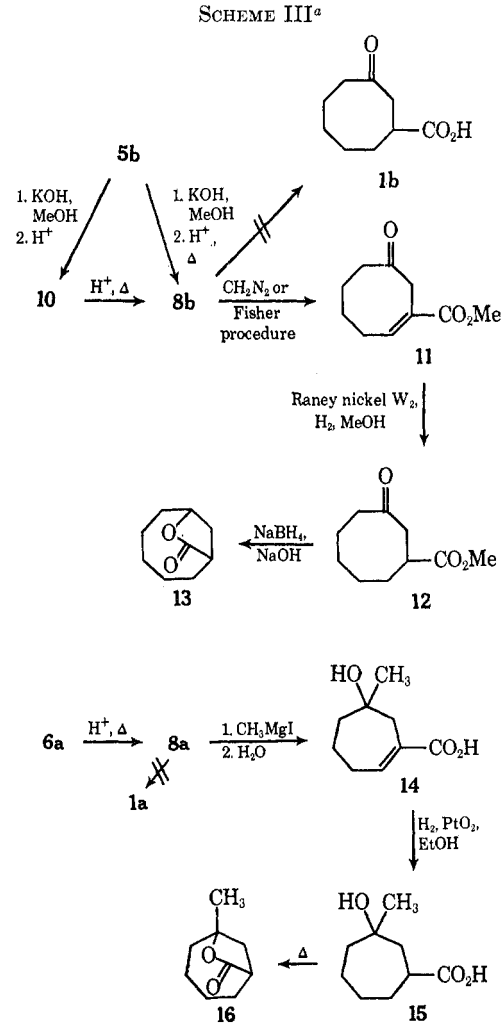
Having succeeded only in preparing the 3-carboxycycloalkanones with even ring sizes in good yield and purity, the challenge remained to prepare the odd ring size analogs. Isolation of 8-oxo-1-cyclononenecarboxylic acid (**8c**) recalled the work of Bose and coworkers[5] (Scheme II) and Cope and coworkers[12] (Scheme III).

SCHEME II[a]



[a] See ref 12.

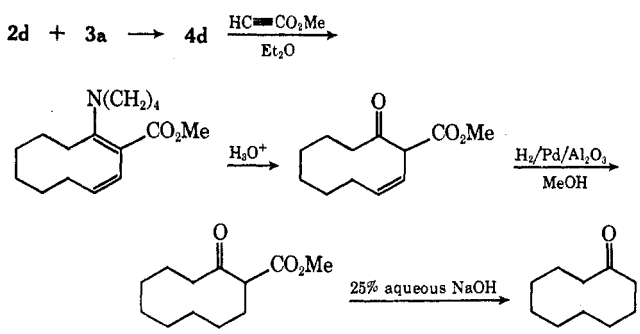
SCHEME III[a]



[a] See ref 5.

(9) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965.

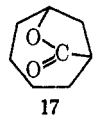
(10) Since completion of this phase of this work, the Pd/Al_2O_3 hydrogenation shown below has been reported by R. Burpitt and J. Thweatt, *Org. Syn.*, **48**, 56 (1968).



(11) R. D. Sands, *J. Org. Chem.*, **34**, 2794 (1969), and earlier papers; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 170, but see a successful alkaline decarboxylation in ref 10.

(12) A. C. Cope, J. M. McIntosh, and M. A. McKervey, *J. Amer. Chem. Soc.*, **89**, 4020 (1967).

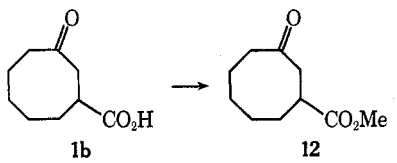
Unfortunately, Cope's group had reported no success on attempted catalytic hydrogenation of either 6-oxo-1-cycloheptenecarboxylic acid (**8a**) or 7-oxo-1-cyclooctenecarboxylic acid (**8b**). Nevertheless, we decided to investigate a sequence **5** → (**6** →) **8** → **1** in the cycloheptane series. 6-Oxo-1-cycloheptenecarboxylic acid (**8a**) was obtained in good yield from the unsaturated diester **6a** by Cope's procedure[12] (refluxing 20% aqueous hydrochloric acid) and, in better yield, directly from the pyrrolidino adduct **5a** (refluxing 10% aqueous hydrochloric acid). Both methods resulted in a product, **8a**, which was contaminated with unsaturated diester **6a** and which was slightly unstable in either reaction mixture. Surprisingly enough, the purified 6-oxo-1-cycloheptenecarboxylic acid (**8a**) could be smoothly hydrogenated (at a faster rate than the unsaturated keto dicarboxylate esters, **6**) over either prereduced platinum oxide or 5% palladium on carbon in glacial acetic acid at 40 psig. The palladium-catalyzed hydrogenation cleanly produced the desired 3-carboxycycloheptanone (**1a**), while the platinum-catalyzed reaction produced a 2:1 mixture of **1a** and 3-hydroxycycloheptanecarboxylic acid lactone (**17**), which could be separated by chromatography on a silica gel column.



17

Because of this success in the cycloheptane series, the 8-oxo-1-cyclononenecarboxylic acid (**8c**) isolated previously (*vide supra*) was prepared in larger amounts using the aqueous hydrochloric acid reaction conditions, in which it also was slightly unstable. Hydrogenation of **8c** to 3-carboxycyclononanone (**1c**) proceeded smoothly on platinum oxide but inconsistently over the palladium catalyst system.

3-Carboxycyclooctanone (**1b**) was also prepared by this variation of Cope's procedure.[12] Unsaturated diester **6b** was hydrolyzed and decarboxylated in refluxing 20% aqueous hydrochloric acid to 7-oxo-1-cyclooctenecarboxylic acid (**8b**),[13] which was subjected to hydrogenation over palladium to the desired 3-carboxycyclooctanone (**1b**), identical in all respects with that prepared by the modified Berchtold–Uhlig procedure.[2] A sample of 3-carboxycyclooctanone (**1b**) was converted with boron trifluoride–methanol complex[14] to its methyl ester, **12**, a compound identical in its properties with that reported by Cope and coworkers.[12]



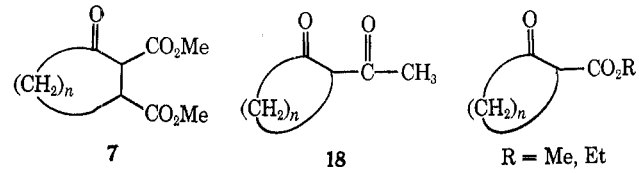
1b **12**

Keto–Enol Equilibria.—Keto–enol equilibria in mesocyclic systems are known to vary markedly with structure and ring size. Paquette and Begland[6] have reported (Table I) 100% enolization for the unsaturated keto diesters **6a** and **6b** and roughly 50% for the larger rings **6c** and **6d**, results which are reinforced by our data.

(13) **8b** may also be prepared directly from the morpholino adduct **5b**: W. A. Meresak, unpublished results.

(14) G. Hallas, *J. Chem. Soc.*, 5770 (1965).

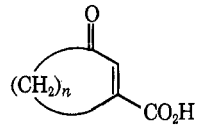
Increased enol content was discovered upon introduction of another double bond into the larger rings or upon replacement of a tetrahedral carbon atom with an oxygen atom. Because of the known flexibility of medium-ring systems[15] and the necessary rigidity associated with the presence of double bonds,[15] it is impossible at the present stage of sophistication to accurately analyze the relative importance of nonbonded interactions, angle strain, and hybridization with respect to one another. The absence of measurable amounts of enol (using proton magnetic resonance spectroscopy) for compounds **8** independent of ring size suggests that the presence of one double bond in a position suitable for conjugation in the enolic form is not sufficient to promote significant enolization in such cycloalkanones. A comparison of the enol content of similar ring sizes in the 2,3-dicarbomethoxycycloalkanones (**7**), the 2-acetylcycloalkanones (**18**),[16] and the 2-carbethoxy- or 2-carbomethoxycycloalkanones (**19**),[17] although measured by different methods with differing precision and accuracy (Table I), suggests slightly decreased enol content upon introduction



7 **18** R = Me, Et **19**

of a 3 substituent (**7** *vs.* **18** or **19**). A Δ^3 double bond does cause an enormous increase in enol content in dimethyl 8-hydroxy-2,8-cyclooctadiene-1,2-dicarboxylate (**6b**) relative to 2,3-dicarbomethoxycyclooctanone (**7b**), but not for the ten-membered ring analog. One can only surmise that decreased nonbonded interactions in the enol of **6b** relative to the enol of **7b** are more significant than in the enol of **6d** relative to the enol of **7d**. Why such a situation exists in the less flexible eight-membered ring and not in the more flexible ten-membered ring is extremely puzzling.

As indicated by Bose and coworkers,[5] it is somewhat surprising that the unsaturated keto carboxylic acids isolated from the hydrolysis and decarboxylation of **6** possess structures **8** to the exclusion of the more highly conjugated isomeric structures **20**. Heap and Whitham[18] have reported the equilibrium compositions for



20

the unsubstituted medium-ring cycloalkanone isomers (Table II). Since the acid-catalyzed decarboxylation of β-keto acids[19,20] is believed to involve the enol of the

(15) J. Dale, *Angew. Chem., Int. Ed. Engl.*, **5**, 1000 (1966); J. D. Dunitz in "Perspectives in Structural Chemistry," Vol. II, J. D. Dunitz and J. A. Ibers, Ed., Wiley, New York, N. Y., 1968, p 1.

(16) Table I, ref *a*.

(17) Table I, ref *b–d*.

(18) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).

(19) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 303.

(20) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 478.

TABLE I
PER CENT ENOL CONTENT

Structure	Ring size 7	8	9	10	Technique	Ref
6	100	100	46	57	Pmr in CCl_4	6
	100	100	31	41	Pmr in $CDCl_3$	6
	100	100		65	Pmr in CCl_4	This work
	100	100		53	Pmr in $CDCl_3$	This work
2-Acetylcycloalkanones (18)	70	95	57	50	Uv	*a*
2-Carbethoxycycloalkanones (19)	31	64	38	70	Pmr in CCl_4	*b*
	14	42	19	49	Titrimetric in EtOH	*c*
	12				Titrimetric in EtOH	*d*
2-Carbomethoxycycloalkanones (19)		40	15	50	Titrimetric in EtOH	*d*
7		30[f]		35[f]	Pmr in $CDCl_3$	This work
1	0	0	0	0	Pmr in $CDCl_3$	This work
8	0	0	0		Pmr in $CDCl_3$	This work
1,3-Cycloalkanediones	0	0	0	10	Various	*e*

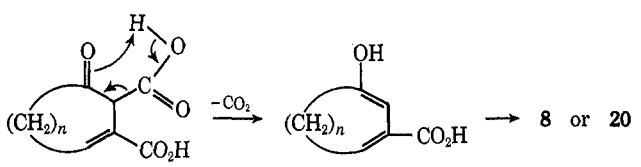
[a] S. Hunig and H. Hoch, *Justus Liebigs Ann. Chem.*, **716**, 68 (1968). [b] S. J. Rhoads, *J. Org. Chem.*, **31**, 171 (1966). [c] S. J. Rhoads and C. Pryde, *ibid.*, **30**, 3212 (1965). [d] G. Schwarzenbach, M. Zimmerman, and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951). [e] I. Maclean and R. P. A. Sneeden, *Tetrahedron*, **21**, 31 (1965); B. Eistert and K. Schank, *Tetrahedron Lett.*, 429 (1964); B. Eistert, F. Haupter, and K. Schank, *Justus Liebigs Ann. Chem.*, **665**, 55 (1963); K. Schank, B. Eistert, and H. J. Felzmann, *Chem. Ber.*, **99**, 1414 (1966). [f] Calculated from area under enol peak relative to total integral.

TABLE II
EQUILIBRIA BETWEEN CYCLOALK-2- AND -3-ENONES[a]

Ring size	Equilibrium composition, % Δ^2	Δ^3
7	73	27
8	20	80
9	<0.3	>99.7

[a] See ref 18.

decarboxylation product, conditions for equilibration of the double bond position would seem to be present prior to the isolation of the products. Inspection of Dreiding models suggests that nonbonded interactions might account for the lack of evidence for **20** as a product in these reactions, particularly as the rings become larger, as suggested by Heap and Whitham.[18] The exocyclic carboxy group does not appear to provide any stabilization which might favor either **8** or **20** relative to the equilibrium composition of the unsubstituted compounds.[18]



Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using 10% solutions in deuteriochloroform, unless otherwise noted, and are reported in parts per million downfield from tetramethylsilane as an internal standard. Only distinct absorptions will be listed herein. Infrared spectra were determined with a Beckman IR-10 spectrophotometer on 5–7% solutions in chloroform unless otherwise specified. Only major absorptions are listed herein. Ultraviolet spectra were measured with a Cary 15 spectrophotometer. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany.

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cycloheptadiene (5a).—This product was prepared in 39.1% overall yield from cyclopentanone by the method of Berchtold and Uhlig[2] and was obtained as white crystals from acetone, mp 144.5–146.5° (lit. 145–146°,[2] 147–148°,[3] 135–138°[4]).

1-(*N*-Morpholino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclooctadiene (5b).—This compound was prepared from cyclohexanone in 32.7% yield by the method of Berchtold and Uhlig[2] and was obtained as a pale yellow solid from acetone, mp 210–212.5° (lit. 210–211°[2], 210–212°[4]).

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclooctadiene (5e).—This compound was prepared from cyclohexanone in 5.7% yield by the method of Berchtold and Uhlig.[2] The poor overall yield[3] results from the 14% conversion of 1-(*N*-pyrrolidino)cyclohexenone (**4e**) to **5e**.

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclononadiene (5c).—This compound was prepared in 37.4% yield from cycloheptanone by the method of Brannock, *et al.*,[3] and was obtained from ether as pale yellow crystals, mp 140–142° (lit. 109.5–110.5°,[3] 139–141°[6]).

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclodecadiene (5d).—This product was prepared in 44.4% yield from cyclooctanone by the method of Brannock, *et al.*,[3] and was obtained from ether as white crystals, mp 104–106° (lit.[6] 104–105°).

Dimethyl 7-Hydroxy-2,7-*cis,cis*-cycloheptadiene-1,2-dicarboxylate (6a).—This compound was prepared from **5a** by the method of Berchtold and Uhlig[2] in 88.5% yield as white, needle-like crystals, mp 60.5–63.0° (recrystallized from 2:1 aqueous methanol) (lit. 63.5–64.0°,[2] 61–62°,[6] 55–57°[3]), spectra in agreement with those reported.[6]

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.37; H, 6.24. Found: C, 58.23; H, 6.23.

Dimethyl 8-Hydroxy-2,8-*cis,cis*-cyclooctadiene-1,2-dicarboxylate (6b).—This product was prepared from **5b** by the method of Berchtold and Uhlig,[2] and was obtained as a 91.9% yield of white needle-like crystals, mp 75.0–77.5° (lit. 75.4–76.3°,[2] 74–75°,[6] 74–75°,[3] 60–64°[4]), spectra as reported.[6]

Anal. Calcd for $C_{12}H_{16}O_5$: C, 60.00; H, 6.70. Found: C, 60.11; H, 6.73.

Identical material was obtained by the same procedure from the pyrrolidino compound **5e** in 79.6% yield.

Dimethyl 10-Hydroxy-2,10-*cis,cis*-cyclodecadiene-1,2-dicarboxylate (6d).—This compound was prepared from **5d** by the method of Berchtold and Uhlig[2] and was obtained as a 68.3% yield of pale yellow, slightly gummy solids. Recrystallization from 1:2 aqueous methanol resulted in a 60% recovery of white, needle-like crystals: mp 55–59°; ir 1750, 1710, 1650, 1600 cm^{-1} [lit.[6] (CCl_4) 1765, 1725, 1655, 1606 cm^{-1}]; uv max (C_6H_{12}) 254 mμ (ε 9800) [lit.[6] 255 mμ (ε 5330)]; nmr δ 3.67 (s, 3), 3.75 (s, 3), 4.64 (s, 0.46), 6.14 (m, 1,) 12.30 (s, 0.53), 53% enol[3] (lit.[6] δ 3.74, 3.83, 4.73, 6.30, 12.45, 41% enol); nmr (CCl_4), δ 3.71 (s, 3), 3.82 (s, 3), 4.58 (s, 0.65), 5.98 (d, J = 4 Hz), 6.20 (d, J = 4 Hz), 12.33 (s, 0.35), 65.4% enol (lit.[6] δ 3.67, 3.78, 4.59, 6.18, 12.33, 57% enol).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.53. Found: C, 63.03; H, 7.40.

Crude product recrystallized from 3:1 aqueous methanol produced a 67% yield of a crystalline product identical with that reported above except for an additional large nmr singlet absorption at δ 1.85, a 55% enol content in $CDCl_3$, uv max (C_6H_{12}) 257 mμ (ε 11,516), and a higher retention factor on tlc analysis on silica gel plates.

Dimethyl 7-Oxocycloheptane-1,2-dicarboxylate (7a).—A solution of 9.6 g (43 mmol) of **6a** in 12 ml of glacial acetic acid was

hydrogenated at 15 psig at room temperature using 96.8 mg of prereduced platinum (IV) oxide (Engelhard) until hydrogen absorption ceased (106% theoretical). The catalyst was removed by filtration, and the filtrate was neutralized ($NaHCO_3$) and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 6.8 g of a viscous, colorless oil, bp 126–132° (0.5–0.6 mm). Gas chromatographic analysis[21] indicated three components at 77, 20, and 3% approximate concentration levels. The effluent from the main peak was collected and found to be impure **7a** by spectral analysis. Attempts to prepare this compound by other hydrogenation routes gave lower yields of impure material.

Dimethyl 8-Oxocyclooctane-1,2-dicarboxylate (7b).—A solution of 2.40 g (10 mmol) of **6b** in 30 ml of glacial acetic acid was hydrogenated over 502.4 mg of prereduced platinum(IV) oxide at 40 psig at room temperature. The reaction was stopped after 125% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The concentrated filtrate was extracted with ether, and the ether layer was dried ($MgSO_4$), concentrated, and distilled at reduced pressure. The lower boiling fraction, 1.34 g (55.4%) of a viscous, colorless oil, bp 123–125° (0.4 mm), contained starting material, product **7b**, and a lactone by spectral analysis. The higher boiling fraction, 0.38 g (15.7%) of a viscous, colorless oil, bp 125–127° (0.4 mm), contained product and a considerable amount of the lactonic byproduct.

The lower boiling fraction was separated in an inefficient manner on a silica gel (Woelm) column using benzene–acetone mixture as eluent. The desired product, **7b**, was isolated as a colorless, viscous oil: ir 1735, 1710, 1650, 1615 cm^{-1}; nmr δ 3.63–3.74 (3 peaks, 6), 12.41–12.52 (two, d, 0.29), enol content[22] 30%.

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.40; H, 7.34.

The lactone was isolated from the later fractions of the column chromatography as a pure compound and identified as 2-carbomethoxy-3-hydroxycyclooctanecarboxylic acid lactone (**9**). After recrystallization from ether, **9** exhibited mp 88–90°; ir 1770, 1740 cm^{-1}; nmr δ 2.04 (broad s, 2), 3.74 (s, 5), 4.95 (m, 1).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.10; H, 7.91.

Hydrogenation of **6b** under these conditions to 100 or 200% of the theoretical hydrogen untake did not improve the conversion of **6b** to **7b**.

Dimethyl 10-Oxocyclodecane-1,2-dicarboxylate (7d).—A solution of 25.6 g (95.4 mmol) of **6d** in 285 ml of glacial acetic acid was hydrogenated over 4.75 g of prereduced platinum(IV) oxide at 40 psig at room temperature until hydrogen absorption ceased (93.5% theoretical). The catalyst was removed by filtration and the acetic acid by distillation under reduced pressure. Distillation of the residue through a Vigreux column gave 22.05 g (85.7%) of a viscous oil: bp 139–140° (0.3 mm); ir 1810, 1730, 1710, 1650, 1605 cm^{-1}; nmr δ 3.60–3.75 (complex pattern, 6.5), 12.70 and 12.80 (two d, 0.36), enol content 35%.[22]

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.08; H, 8.06.

6-Oxo-1-cycloheptenecarboxylic Acid (8a). Method 1.—A solution of 5.0 g (1.79 mmol) of **5a** in 100 ml of 10% HCl was refluxed for 16 hr, cooled to 0–2°, and aged overnight. Fine, amorphous, brown solids (0.2 g) were removed by filtration. The filtrate was extracted three times with ether and the combined ethereal extracts were dried ($MgSO_4$) and partially concentrated under reduced pressure. The resulting slurry was filtered to give, after drying overnight at reduced pressure, 1.10 g (39.7%) of white, needle-like crystals: mp 73–75° (lit.[12] 73.5–75.0°); ir 1710, 1690, 1640 cm^{-1} (as reported[12]); nmr δ 3.65 (s, 2), 7.35 (t, 1, J = 5.0 Hz), 11.30 (s, 1) (as reported[12]).

Anal. Calcd for $C_{18}H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.62; H, 6.59.

Evaporation of the ethereal liquors gave 0.8 g of waxy orange solids whose spectra indicated the presence of **6a** along with the desired **8a**.

Method 2.—This product (**8a**) was prepared from **6a** by the method of Cope, *et al.*,[12] and was obtained as a 23.4% yield of pale yellow crystalline agglomerates, mp 68.0–71.5°, with spectra identical with those reported above. Evaporation of the mother liquors resulted in a clear amber oil consisting of a mixture of **6a** and **8a**.

7-Oxo-1-cyclooctenecarboxylic Acid (8b).—A solution of 9.8 g (40.7 mmol) of **6b** in 41 ml of 20% HCl was refluxed for 8 hr, cooled to 0–2°, and aged for 1 hr. The resulting slurry was filtered and washed exhaustively with H_2O. The tan solids were dried overnight at 39° under reduced pressure to give 4.3 g of product, and an additional 1.0 g was obtained from CH_2Cl_2 extracts of the mother liquors taken to dryness. Combined crops were recrystallized from benzene to produce 3.84 g (63.5% yield) of **8b**: mp 103.0–105.0° (lit.[12] 108–109°); ir 1700–1680, 1645 cm^{-1} (as reported[12]); nmr δ 3.45 (s, 2), 7.20 (t, 1, J = 9.0 Hz), 11.16 (s, 1) (similar to reported data[12]).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.06.

8-Oxo-1-cyclononenecarboxylic Acid (8c).—A solution of 7.7 g (25 mmol) of **5c** in 154 ml of 10% HCl was refluxed for 20 hr, cooled to 0–2°, and aged for 2 hr. The resulting slurry was filtered and washed exhaustively with ice water. Tan needle-like crystals (3.4 g, 74.3%) were obtained after drying overnight at 39° and reduced pressure. A sample recrystallized from ether exhibited mp 111.0–112.5°; ir 1695, 1640 cm^{-1}; nmr δ 3.54 (s, 2), 7.22 (t, 1, J = 8.5 Hz), 11.45 (s, 1).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.75. Found: C, 65.69; H, 7.94.

Extraction of the mother liquors with ether followed by drying of the ethereal extract ($MgSO_4$) and removal of the ether gave 0.6 g of pale yellow needles, spectra identical with those of desired product except for a small nmr absorption at δ 3.78 (s, 0.2).

3-Carboxycycloheptanone (1a).—Hydrogenation of a solution of 1.00 g (6.5 mmol) of **8a** in 15 ml of glacial acetic acid at room temperature and 40 psig over 100 mg of prereduced platinum(IV) oxide was performed until hydrogen absorption ceased (142% theory). After removal of the catalyst by filtration and the acetic acid by distillation under reduced pressure, the residue was dissolved in ether and dried ($MgSO_4$). The ether was removed and the residue distilled to give 0.64 g of a viscous colorless oil, bp 120–130° (0.2 mm), which partially solidified. Tlc indicated the presence of two components.

A solution of 0.418 g of the above material in chloroform was separated into two components by column chromatography on silica gel (Davison Chemical). The first material obtained was 0.109 g of a white, waxy solid. A 50-mg portion of this solid was sublimed at room temperature and 0.2 mm to give 41 mg of 3-hydroxy-cycloheptanecarboxylic acid lactone (**17**), a white crystalline solid: mp 102–104°; ir 1760 cm^{-1}; nmr δ 4.90 (broad d, 1).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.76.

The second component was 0.236 g of the desired **1a**, a viscous, clear, colorless oil: ir 1705 cm^{-1}; nmr δ 8.95 (s, 1) [lit.[2] bp 200° (0.65 mm); mp 40–41°; ir 1700, 1550 cm^{-1}].

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.34; H, 7.80.

The desired product **1a** was also prepared from the hydrogenation of 0.882 g (5.13 mmol) of **8a** in 12 ml of glacial acetic acid at 40 psig and room temperature over 88.5 mg of 5% palladium on carbon (Engelhard). The same work-up as above (without the chromatography) produced 0.569 g (64.4%) of pure **1a** as a clear, slightly yellow oil, bp 120–121° (2 mm), with spectra identical with those exhibited by the material purified by chromatography (*vide supra*).

3-Carboxycyclooctanone (1b). Method 1.—A solution of 0.80 g (4.75 mmol) of **8b** in 10 ml of glacial acetic acid was treated with hydrogen at 40 psig and room temperature over 100 mg of 5% palladium on carbon until hydrogen absorption ceased (139% theoretical). The catalyst was removed by filtration and the filtrate concentrated at reduced pressure. An ethereal solution of the residue was dried ($MgSO_4$) and evaporated to dryness under reduced pressure, leaving 0.73 g (90.5%) of white, crystalline solids: mp 96.5–100.0°; ir 1705 cm^{-1}; nmr δ 10.51 (s, 1).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.39.

Method 2.—A solution of 29.0 g (0.120 mol) of the low-boiling fraction of impure **7b** in 250 ml of 10% HCl was refluxed for 28 hr and the solvent removed by distillation at reduced pressure. The residue was dissolved in ether, dried ($MgSO_4$), and concentrated under reduced pressure to a heavy slurry. After aging for 2 hr at 0–2°, the slurry was filtered and the cake washed with

(21) A 6 ft × 0.25 in. 3% SE-52 column at 170° on F & M Series 810 gas chromatograph.

(22) Enol content was calculated from the area under the enol absorptions relative to the total pmr integral.

0–2° ether to give 9.55 g (46.1%) of white, crystalline **1b**. The ir and pmr spectra of this solid, as well as the behavior on tlc, presented evidence for the presence of 7-oxo-1-cyclooctenecarboxylic acid (**8b**) as an impurity, even though elemental analysis was satisfactory for pure **1b**.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.42; H, 8.09.

Hydrogenation of 1.703 g of this solid material as in method 1 (above) produced 1.601 g (94.0%) of white, crystalline solids corresponding to pure **1b**: mp 96.5–100.0°; ir 1705 cm^{-1}; nmr δ 10.51 (s, 1).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.61; H, 8.38.

3-Carbomethoxycyclooctanone (**12**).—A solution of 2.00 g (11.7 mmol) of **1b** in 10 ml of methanol was refluxed for 2 hr with 40 ml of 1:2 BF_3–MeOH complex[14] under a nitrogen atmosphere. The solution was cooled, poured into $CHCl_3$, extracted with H_2O, washed with saturated NaCl solution, dried ($MgSO_4$), concentrated, and distilled under reduced pressure to give 1.82 g (84.1%) of a colorless oil: bp 74–75° (0.25 mm); ir 1730, 1700 cm^{-1} (as reported[12]); nmr δ 3.67 (s, 3) (as reported[12]).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.06; H, 8.87.

3-Carboxycyclononanone (**1c**).—A solution of 0.85 g (4.56 mmol) of **8c** in 25 ml of glacial acetic acid was hydrogenated at 40 psig and room temperature over 180 mg of prereduced platinum-(IV) oxide until hydrogen absorption ceased (136% theoretical). Work-up as for **1b** (method 1) above gave 0.48 g (55.9%) of a viscous, clear and colorless oil: bp 135–136° (0.2 mm); ir 1700 cm^{-1}; nmr δ 10.30 (s, 1). This oil solidified to a waxy, white solid after storage overnight at 4°.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.98.

Similar results were produced on hydrogenation of **8c** over 5% palladium on carbon except that the product **1c**, was contaminated with unreacted starting material even after repeated hydrogenation.

3-Carboxycyclodecanone (**1d**).—Hydrolysis and decarboxylation of **7d** was performed by refluxing 20.7 g (76.5 mmol) of **7d** in 250 ml of 10% HCl for 29 hr. Most of the H_2O was removed under reduced pressure. The residue was dissolved in ether, dried ($MgSO_4$), and concentrated under reduced pressure to a heavy slurry, from which 15.8 g (104%) of waxy material was separated by filtration. Recrystallization from ether gave 9.25 g (60.9%) of white crystalline solids: mp 56.0–58.5°; ir 1700 cm^{-1}; nmr δ 11.20 (s, 1).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.48; H. 9.06.

The ethereal mother liquors were concentrated further to give 1.45 g (9.5%) of white solids identical in all respects with the above product.

Registry No.—**1a**, 27531-68-6; **1b**, 27531-69-7; **1c**, 27531-70-0; **1d**, 27531-71-1; **6d**, 27531-72-2; **7a**, 27531-73-3; **7b**, 27531-74-4; **7d**, 27531-75-5; **8a**, 17606-97-2; **8b**, 17606-93-8; **8c**, 27531-78-8; **9**, 27531-79-9; **12**, 17606-96-1; **17**, 18543-37-8.

Absolute Configurations of the *p*-Menthane-2,5-diones and *p*-Menthane-2,5-diols[1]

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The eight diastereoisomeric *p*-menthane-2,5-diols (**1–8**), the four diastereoisomeric *p*-menth-1-ene-3,6-diols (**9–12**), and the two (+)-*p*-menthane-2,5-diones (**13** and **14**), which all have the same absolute configuration at the isopropyl group as (−)-α-phellandrene (**15**), have been prepared, characterized, and interrelated. Absolute configurations have been established for **1–14** by stereoselective chemical interconversions, including hydrogenation of diols **9–12**, Jones oxidation of diols **1–6**, lithium aluminum hydride reduction of diones **13** and **14**, and displacements by formate and hydride ions on monotosylates of diol **4**.

The configurational assignments presented here for the optically active *p*-menthane-2,5-diones and *p*-menthane-2,5-diols formed the basis of our previous definitive report on the *p*-menth-1-ene-3,6-diols.[2] The configurational relationships among the eight diastereoisomeric *p*-menthane-2,5-diols (**1–8**), the four diastereoisomeric *p*-menth-1-ene-3,6-diols[2] (**9–12**), and the two (+)-*p*-menthane-2,5-diones (**13** and **14**), which all have the same absolute configuration at C-4 as (−)-α-phellandrene (**15**), are shown in Scheme I.

Racemic Diones and Diols.—Racemic mixtures containing diones **13** and **14** and diols **3** and **4** have been prepared previously. Lithium–liquid ammonia–ethanol reduction of 2,5-dimethoxy-*p*-cymene followed by acid-catalyzed hydrolysis of the reduction product gave in 96% yield an equilibrium mixture of diones (±)-**13** and (±)-**14**, from which the more stable isomer, (±)-*cis*-*p*-menthane-2,5-dione [(±)-**13**], mp 72–73°, was isolated by fractional crystallization.[3] Hydrogenation of dione (±)-**13** gave (±)-*cis,cis,cis*-*p*-menthane-2,5-diol [(±)-**3**], mp 105°. Assignment of the all-cis configuration, (±)-**3**, to the racemic diol, mp 105°, was based unequivocally upon infrared spectroscopic studies of intramolecular hydrogen bonding.[3,4] Among the *p*-menthane-2,5-diols with hydroxyl groups cis to one another (**1–4**), only diol **3** exhibits detectable intramolecular hydrogen bonding.[4] Diol (±)-**3** has also been prepared by hydrogenation of thymoquinone with rhodium on alumina catalyst at 25°.[5] In addition, a (±)-*p*-menthane-2,5-diol, mp 144°, was isolated from the product of reduction of thymoquinone.[5] The cis configuration of the more stable racemic dione [(±)-**13**], mp 72–73°, was confirmed by its preparation by stereospecific Jones oxidation[6] of the all-cis diol (±)-**3**.[5] Jones oxidation[6] of the racemic diol, mp 144°, gave (±)-*trans*-*p*-menthane-2,5-dione [(±)-**14**], mp 43–43.5°.[5] Therefore, the racemic diol, mp 144°,

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