THE PREPARATION AND SPECTRAL STUDIES OF A SERIES OF CYCLIC β -KETOESTERS¹

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Abstract—2-Carbethoxycyclanones of ring size 5–12 and 15 and their C-methyl derivatives have been prepared and studied in the U.V. and I.R. spectral regions. The enolizable β -ketoesters show a high intensity K band in the 255–263 m μ region associated with the chelated enolic species and two pairs of bands in the 6 μ double bond stretching region which correspond to the structural features of the keto and enol tautomers. The non-enolizable β -ketoesters show only a low intensity R band in the 280– 300 m μ region and one pair of bands in the 6 μ region. Correlations of the spectral properties have been made with enol content and with structural characteristics of the ring systems. Trends in the characteristic I.R. frequencies of the chelated enols have been noted and interpreted in terms of the geometry of the chelate structure.

As a part of a general study directed towards assessing the importance of steric factors in reactions of carbanions, we have chosen first to examine the properties and reactions of cyclic β -ketoesters derived from the common and medium ring systems. Our choice stemmed from the hope that the peculiar steric requirements of the medium ring compounds which predispose them to unusual reactivities in their "carbonium chemistry"⁹ might also be manifested in those reactions and properties which depend upon the intermediacy of carbanions. Within a series of cyclic β -ketoesters, one may reasonably look for the appearance of these effects in terms of acidity and enolization tendency and of rate and direction of alkylation. The following paper⁴ reports on the effects of ring size on acidity and rate of C-alkylation in the series;⁶ the present paper is concerned with the preparation and spectral characteristics of the 2-carbethoxycyclanones (I) and their C-methyl derivatives (II)



- ¹ Abstracted in part from the B.S. (Honors) Thesis of J. C. G., University of Wyoming, June, 1961 and from the Ph.D. Dissertation of A. W. D., University of Wyoming, June, 1962.
- ⁸ American Chemical Society Scholars, 1959-62.
- ^a See J. Sicher, *Progress in Stereochemistry* (Edited by P. B. D. de la Mare and W. Klyne) Vol. 3, p. 222 ff. Butterworths, Washington (1962) for a timely review.
- ⁴ S. J. Rhoads and A. W. Decora, Tetrahedron, 1645, (1963).
- ^b Studies are presently in progress on the effect of ring size on the direction (C- vs. O-) of alkylation. For earlier work on this problem see S. J. Rhoads, R. D. Reynolds, and R. Raulins, J. Amer. Chem. Soc. 74, 2889 (1952).

Preparation and characterization

The 2-carbethoxycyclanones of the medium (n = 8-12) and large (n = 15) rings are conveniently prepared by carbethoxylation of the corresponding ketones by means of diethyl carbonate (used in large excess) and two equivalents of sodium hydride at room temperature. This method, which appears to be quite general for ketones of low acidity, is recommended for its relative simplicity, the excellence of its yields, and the purity of the products-factors which become increasingly important as the ketonic starting materials become more dear.

The β -ketoesters prepared in this manner were mobile to viscous liquids at ordinary temperatures and showed chemical behavior and spectral properties typical of such systems. The presence and, roughly the relative abundance of enolic modifications in all members of the series are indicated by their response to ferric chloride and copper acetate reagents. With Henecka's ferric chloride reagent,⁶ an instantaneous and intense coloration (blue to blue-purple) appears with the compounds I-5 through I-10; thereafter in the series, the color develops more slowly and is diminished in intensity. Corresponding results are observed when the complexing powers of the β -ketoesters with copper ion are compared. In the latter case, the extent of complex formation as judged by the intensity of the dark green coloration and by the degree of crystallization of the copper derivative from solution roughly parallels the acidities of the β -ketoesters.^{4,7} Table 1 summarizes these various data and provides corresponding results for two acyclic analogs, ethyl α -ethylacetoacetate (III) and ethyl 2-(n-hexyl)-3-keto-decanoate (IV).



Methylation of the β -ketoesters of ring size five through eight may be carried out in the conventional way with ethanolic sodium ethoxide and methyl iodide. With the larger ring derivatives, however, conventional methylations are slow and incomplete because of the very low acidities of these compounds. For these β -ketoesters it is advantageous to resort to a slurry of sodium hydride in benzene for the formation of the carbanion; in this way, methylation can be forced essentially to completion and contamination by unreacted β -ketoester, which is very difficult to remove, can largely be avoided. The structures and the purities of the C-methylated products were established by their I.R. and U.V. spectra, their g.l.p.c. (gas-liquid-partitionchromatography) patterns and by hydrolysis and decarboxylation to the corresponding 2-methylcyclanones (Tables 3, 8 and 9.)

Ultraviolet spectra

The U.V. absorption spectra of the 2-carbethoxycyclanones (I), their C-methyl derivatives (II) and the open chain β -ketoesters (III and IV) were measured in ethanol

⁶ H. Henecka, Chemie der beta-dicarbonyl-verbindungen p. 111. Springer-Verlag, Berlin (1950).

⁷ These same facts were remarked by W. Dieckmann for I-5, I-6 and I-7 in his classical investigation of cyclic β-ketoesters in 1901 [(W. Dieckmann, *Liebigs Ann.* 317, 27 (1901)].

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TABLE

		Mathod a	Analy	sis	Ę	
β -Ketoester	B.P. (°/mm)	and Yield	Calc'd for CaHın_4O3	Found	Reagent	Cu(OAC), Reagent
I-5	116-121/22	A , 83%	- 		+++++++++++++++++++++++++++++++++++++++	•(XXX) ++++
I-6	107-109/14	B, 50%	٩ ا	1	• +	(XX) + + +
1-7	122-124/9	C, 8, 5	٩	1	· + · +	(XX) + + +
I-8	124-126/8	C, 75%	C, 66-4	C, 66-8	- + - + - +	(X) ++++
			H, 9-2	H, 9-1		
6-1	108110/2	C, 87%	C, 67-9	C, 68·1	++++	++
			H, 9-5	H, 9.6		
I-10	118-120/1	C, 75%	C, 69-0	C, 69-2	++++	++
			H, 9-8	H, 10-1		
11-1	140-143/5	C, 55%	C, 70.0	C, 70-0	++	+ (weak)
			H, 10-1	H, 10-2		
1-12	155-157/3	C, 76%	C, 70.8	C, 71·1	+ (slow, weak)	+ (weak)
			H, 10-3	H, 10-4	•	
I-15	168-169/1	C, 81%	C, 72-9	C, 73·3	+ (slow, weak)	+ (weak)
			H, 10-9	H, 11-0		•
III	117-118/70	D, 55%	و ا	I	+ (slow, weak)	+ (weak)
N	172-174/5	E, 69 %	7	1	+ (slow, v. weak)	+ (v. weak)
• Method A: Or Method B: Or Method C: Ca	g. Syn. Coll. Vol. II, I g. Syn. Coll. Vol. II, F	p. 116. 5. 531.	the second se			

Method C: Carbenoxylation of cyclanone by dietnyl carbonate-sodium hydride method. See text and experimental Method D: Ethylation of ethyl acetoacetate by conventional procedure. Method E: Sodium hydride induced Claisen condensation of ethyl occanoate. $^{\circ}$ 1% solution of anhyd. FeCl_s in anhyd. CH_sOH. Comparative intensities are indicated by (+) for solutions of the same concentrations. • Saturated solution of Cu(OAc)₂ 2H_sO in ethanol.

Known compound.
(X) indicates that crystallization of copper derivative occurs under test conditions.

and in cyclohexane. The data are shown in Tables 2 and 3. The enolizable β -ketoesters (Table 2) show maxima and extinction coefficients in the region 255-263 m μ associated with the high intensity K band of the chelated enolic tautomer (IE).⁸ The low intensity R band of the keto form (IK) which lies in the region 280-300 m μ , is



completely masked by the high intensity band in those β -ketoesters of appreciable enol content (I-6 through I-10) even in the solvent ethanol which shifts the equilibrium toward the keto tautomer. With those β -ketoesters of low enol content (I-5, I-11, I-12, I-15, III and IV), the spectra in alcohol reveal the presence of the R band of the keto form as a weak shoulder or inflection in the 290-300 m μ region.

Compound	% Enol •	λ_{\max}^{EtOH}	€'EtOH ^b max	$\lambda_{\max}^{0_6H_{13}}$	€' ^{CeH12^b}
I-5	5	255	668	255	3,340
I-6	57	258	6,420	258	10,200
I-7	12	264	1,625	264	7,100
I-8	40	262	4,820	262	7,860
I-9	15	262	2,340	262	6,700
I-10	50	261	5,660	261	9,550
I-11	9	263	770	263	1,320
I-12	5	261	418	261	826
I-15		261	352	261	774
III	3	259	236	259	722
IV		263	239	263	592

TABLE 2. ULTRAVIOLET ABSORPTION DATA FOR ENOLIZABLE β -KETOESTERS

^a Data on enol content are taken from the work of Schwarzenbach, Zimmerman and Prelog.,¹¹ and J. B. Conant and A. F. Thompson, *J. Amer. Chem. Soc.* 54, 4039 (1932) and are for dilute alcoholic solutions.

^a Average equilibration time, 8 days.

The effect of solvent polarity on the position of equilibrium in tautomeric systems of the sort involved here has been recognized for many years and has been attributed to the difference in polarity of the keto form and the chelated enol.⁹ It is noteworthy that in all the cases examined in the present study, an enhancement of enol content is observed with a solvent change from ethanol to cyclohexane. The implication is strong that the only important enolic variety in all these cases is a *cis* enol which owes

⁹ G. W. Wheland, Advanced Organic Chemistry 3rd Edition, p. 680. John Wiley, New York (1960).

⁸ A. E. Gillam and E. S. Stern, An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry p. 111 ff. Edward Arnold, London (1954).

its stability to intramolecular hydrogen bonding.¹⁰ Substantiation of this view is found in the I.R. spectra of these compounds discussed later in this paper. The degree of response to solvent change in terms of enol content through the series is also of interest. The five-membered ring compound shows the most dramatic change in this respect; the enol content, as measured by the apparent extinction coefficient, ϵ' , increases some five-fold in passing from the solvent ethanol to the solvent cyclohexane

	Ethanol			Cyclohexane				Δλ	
Compound	λ _{max}	€	λ _{min}	ε	λ_{max}	ε	λ_{\min}	e	$(\lambda_{\max}^{C_{6}H_{1}} - \lambda_{\max}^{RtCH})$
II-5	295	40	253	8	299	37	255	7	+4
II-6	284	28	252	17	292	26	255	14	+-8
II-7	288	28	252	10	293	28	253	10	+5
II-8	291	31	254	15	294	33	254	15	+3
II-9	288	41	258	25	292	34	254	15	+4
II-10	289	38	254	21	293	36	253	18	+4
II-11	288	38	252	14	290	38	253	14	+2
II-12	288	44	252	13	288	52	255	37	0
II-15	284	58	255	37	282	50	254	36	-2
C-CH ₃ derivative									
of IV	283	57	255	33	284	49	254	24	+1

TABLE 3. ULTRAVIOLET ABSORPTION DATA FOR NON-ENOLIZABLE β -ketoesters ^a

• Wavelengths in $m\mu$.

(Table 2). In contrast, I-11, I-12, I-15 and the open chain compound IV, all of which in ethanol show low enol contents of the same order of magnitude as that of I-5,¹¹ respond to the solvent change by a factor of less than 2.5. It seems likely that these differences can be traced to a decrease in the polarity difference between correponding tautomers as the size of the molecular system increases.¹² Also noteworthy is the insensitivity of the position of the maximum of the enolic absorption to solvent change. Such behavior is characteristic of non-polar solutes¹² and contrasts with the behavior noted for the non-enolizable β -ketoesters (Table 3). Finally, it should be pointed out that qualitative conclusions concerning the relative enol content in this series of β ketoesters as deduced from the apparent extinction coefficients (Table 2) accord with the enol measurements reported by others. In particular, Schwarzenbach *et al.*¹¹ reported the enol contents for a series of cyclic β -ketoesters in dilute alcoholic solution. The ring systems studied by these workers were the same as those reported here,

¹⁰ M. I. Kabachnik, S. T. Joffe, E. M. Popov, and K. V. Vatsuro, *Tetrahedron* **12**, 77 (1961) have recently asserted that steric pressures in the form of bulky α -substituents cause a preference for a *trans* geometry in the enols of such β -ketoesters. Such a structure would not, of course, show the solvent response of the non-polar, chelated *cis* enol and indeed would be expected to respond in an opposite manner. In view of the demonstrated change-over in relative *cis/trans* olefin stability in the medium ring compounds between the 10 and the 11 carbon cycles [A. C. Cope, R. T. Moore and W. R. Moore, *J. Amer. Chem. Soc.* **81**, 3153 (1959)] it seemed a real possibility that *trans* enolization might occur in the larger ring β -ketoesters as well as in III and IV; however, no evidence supporting this possibility has been found in the present study. To the extent that enols do exist in these systems, they have the properties of the *cis*, chelated structure.

¹¹ G. Schwarzenbach, M. Zimmerman, and V. Prelog, Helv. Chim. Acta 34, 1954 (1951).

¹⁸ Ref. 8, p. 265.

except that methyl esters were employed for those derivatives of ring size >8. These data are reproduced in Table 2 and show reasonably good agreement with the changes in ϵ' in the series.¹³

The spectral data for the non-enolizable β -ketoesters shown in Table 3 reveal the low intensity R band ($\epsilon = 30-60$) of the ketonic absorption in the region 280-300 m μ . The minima are also recorded in Table 3 and confirm the high purities of the compounds listed.¹⁴ The last column of Table 3 shows the effect of the solvent change from



FIG. 1. Ultraviolet spectra of I-12 and II-12 in ethanol.

ethanol to cyclohexane on λ_{max} . These small shifts of the R band to longer wave length with a change to a less polar solvent are characteristic of carbonyl compounds which possess some polar character¹² and may be compared with the indifference to solvent change of the less polar chelated enols mentioned earlier. The decreasing sensitivity toward solvent polarity as the molecular weight increases in the series (cf. II-12 etc.) is also in accord with the notion of decreasing polarity within the series of ketoesters.¹⁶

Figure 1 shows the U.V. absorption curves for I-12 and II-12 in ethanol which are illustrative of the points discussed in the preceding paragraphs.

- ¹⁸ Such discrepancies as do appear may be due to the fact that the implicit assumption that the true extinction coefficients for the enols are all of the same order of magnitude in the series (ca. 12,000) is unjustified or that insufficient time was allowed for equilibration before the titrations were carried out. We have found that equilibrium between the tautomers is established quite slowly, especially with the larger molecules, and in many cases requires as much as one week at room temperature. Bromometric determinations of the enol contents in this series are presently being carried out in our laboratories.
- ¹⁴ The presence and intensity of the minima in these compounds are very sensitive indicators of the absence of contaminating I since the minima in II represent regions of high absorption in I. For example, from the absorption curve of I-12, 6¹⁵⁰/₅₅₅ = 355, from which is may be calculated that the maximum contamination of I-12 in II-12 is 3.7 per cent. For compounds of type I with higher enol content than I-12, the intensity of the minimum is an even more sensitive indication of purity. The absence of appreciable amounts of I in samples of II was shown by their g.l.p.c. patterns.
- ¹⁸ Questions of conformational isomers in these compounds and their relative abundance in solvents of differing polarity also arise [cf. R. C. Cookson, J. Chem. Soc. 282 (1954); E. M. Kosower and G.-S. Wu, J. Amer. Chem. Soc. 83, 3142 (1961); E. M. Kosower, G.-S. Wu, and T. S. Sorensen, *ibid.* 83, 3147 (1961).] However, the shifts in λ_{max} observed when these compounds are compared with the parent ketones in the same solvents are so small that speculation on this point seems fruitless at this time. Cf. the similar problem in the I.R. spectra.

Infrared spectra

Scattered data on the I.R. absorption characteristics of open chain and cyclic β -ketoesters have been reported in earlier investigations.^{16–19} In the most extensive examination of cyclic β -ketoesters reported to date, Leonard *et al.*¹⁷ investigated the spectra of a number of β -ketoesters derived from six- and five-membered cyclic systems. For enolizable compounds, these workers recognized four bands in the 6 μ region which they attributed to the ester and ketone carbonyl stretching modes of the (non-conjugated) ketoester (IK) and to the conjugated ester carbonyl and conjugated carbon-carbon double bond stretchings of the chelated enolic tautomer (IE). The lack of characteristic absorption bands in the 3 μ region which could be traced either to free (non-chelated) OH or to chelated OH vibrations was taken as evidence that the enolic species of these compounds "occurs primarily as the chelated form in which the hydroxyl OH is perturbed beyond recognition."²⁰

The characteristic absorption bands in the 6 μ region found for the compounds studied in the present investigation are summarized in Tables 4 and 5 and are shown in Figs. 2 and 3. Our findings confirm and extend the generalizations outlined by Leonard *et al.* For the enolizable β -ketoesters (Table 4), four bands appear in the double bond stretching region, a pair at higher frequency (1760–1710 cm⁻¹) associated with the keto tautomer and a lower frequency pair (1665–1600 cm⁻¹) due to the chelated enol. As expected, the relative intensities of these two sets of bands vary with enol content; a change of state from the pure liquid to solution in tetrachloroethylene (TCE) produces intensification of the low frequency bands as the equilibrium shifts in the direction of the enol. Moreover, the relative intensities of the band pairs vary throughout the series according to the reported enol contents¹¹ and the patterns already noted in the ultraviolet spectral work (cf. Fig. 2). The non-enolizable β -ketoesters, II, show only the higher frequency bands in the 1760–1710 cm⁻¹ region and are essentially transparent in the 1660–1600 cm⁻¹ region.

The band assignments made in Tables 4 and 5 follow those of Rasmussen and Brittain¹⁶ and Leonard *et al.*¹⁷ with one notable exception. In the case of 2-carbethoxy-cyclopentanone (I-5), the latter workers assigned the 1757 cm⁻¹ band (reported,¹⁷ 1756 cm⁻¹) and the 1730 cm⁻¹ band (reported,¹⁷ 1725 cm⁻¹) to the carbonyl stretching vibrations of the ester and the ketone functions, respectively. We deem it much more reasonable to reverse this assignment, i.e., to attribute the 1757 cm⁻¹ absorption to the ketone carbonyl and the lower 1730 cm⁻¹ band to the ester carbonyl. Cyclopentanone, itself, as a result of internal strain, absorbs at the abnormally high ketone frequency of 1747–48 cm⁻¹ (Table 6); various 16-keto- and 17-ketosteroids show this same ketone absorption in the range 1740–1754 cm⁻¹ (CS₂).²¹ In view of these

- ¹⁴ R. S. Rasmussen and R. R. Brittain, J. Amer. Chem. Soc. 71, 1073 (1949).
- ¹⁷ N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Peterson, J. Amer. Chem. Soc. 74, 4070 (1952).
- ¹⁸ L. J. Bellamy and L. Beecher, J. Chem. Soc. 4487 (1954).
- ¹⁹ S. Bratoz, D. Hadźi and G. Rossmy, Trans. Faraday Soc. 52, 464 (1956).
- ³⁰ Bratoz *et al.*¹⁹ have also noted the absence of such bands in the spectrum of acetoacetic ester, although a broad band does appear in deuterated acetoacetic ester at 2227 cm⁻¹ [ν_6 (OD)]. In the present study, also, no bands attributable to free or chelated OH were detected in any of enolizable β -ketoesters.
- ^{11a} R. N. Jones, P. Humphries and K. Dobriner, J. Amer. Chem. Soc. 71, 241 (1949); ^b Ibid. 72, 956 (1950).

observations, the position of the ketone absorption in I-5 at 1757 cm⁻¹ does not seem out of line, especially when dipolar interactions are considered. Insofar as the ester frequency is concerned, Jones and Sandorfy²² quote a value of 1740 cm⁻¹ for carbethoxycyclopentane while the bile acid derivatives, methyl etiocholanate and methyl

Compound	54a4a	Keto form		Chelated en	ol form
Compound	State	ν _C =0 ester	v _{C=0 ketone}	ν _C ≠0 ester	v _{c=c}
I-5	liq. TCE CH3CN CHCl3	1730 vs 1730 vs 1723 vs 1725 vs	1757 s 1757 vs 1750 s 1753 s	1661 w 1663 s 1661 w	1622 vw, br 1619 s-m
1-6	liq. TCE CHCl ₃ CH ₃ CN	1744 w 1742 vw, br 1735 vw, br 1740 w, br	1720 w 1719 w 1712 w–m 1712 w	1656 s, br 1655 vs 1657 sh, 1650 s	1618 m 1615 s 1617 m
I-7	liq.	1740 s	1708 s	1638 m	1614 w, br
	TCE	1744–1737 s, br	1711 s	1641 m	1611 m-w
I-8	liq.	1745 m	1709 m	1643 s	1612 m, br
	TCE	1748 w. 1738 sh	1710 m	1646 s	1609 m–s
I-9	liq.	1745 s	1709 s	1641 m	1609 m–w
	TCE	1749 m. 1735 sh	1711 s	1643 m	1608 m–w, br
I-10	liq.	1744 m-s	1711 m-s	1640 m-s	1603 m, br
	TCE	1748 m. 1737 sh	1711 m-s	1642 m-s	1600 m
I-11	liq.	1746 s	1714 s	1641 w, br	1603 w, br
	TCE	1752 s. 1743 sh	1715 s	1644 w–m	1601 w-m
I-12	liq.	1743 s	1714 vs	1641 vw, br	1607 vw, br
	TCE	1748–1737 s. br	1714 vs	1645 w	1604 w
I-15	liq.	1744 s	1713 s	1641 vw	1608 vw
	TCE	1744 s, br	1714 vs	1643 m–w	1608 m–w
III	liq.	1738 s, br	1717 s, 1725 sh	1641 vw	1618 vw
	TCE	1740 s	1720 vs	1650 m-w	1616 w
IV	liq.	1745 s	1718 s	1642 vw	1610 vw
	TCE	1737 vs	1717 ys	1644 m-w	1609 w
ethyl aceto- acetate	liq. TCE	1743 s, br 1750–1742 m, br	1723 s 1730 s	1651 w, br 1660 m–s, 1655 sh	1640 w, br 1637 m–s, 1644 sh

TABLE 4. INFRARED ABSORPTION DATA FOR ENOLIZABLE β -ketoesters^{a,b,c}

^a Liquid samples were examined as capillary films in most cases; occasionally, 0.025 mm thick films were used to intensify very weak peaks. Solutions in TCE, CH₃CN and CHCl₃ were usually 0.02 M and were examined in 1 mm cells. In those cases in which the chelate bands were very weak, more concentrated solutions were employed to intensify and sharpen the bands.

^b s = strong, m = medium, w = weak, v = very, br = broad, sh = shoulder.

• Frequencies in cm^{-1} . Estimated reproducibility, $\pm 2 cm^{-1}$.

etio-allocholanate absorb at 1737-1739 cm⁻¹ (CS₂).^{21b} Since in all these compounds which possess an ester function attached to a five-membered ring, the ester absorption shows a quite normal value, the presumption of the Illinois group that the effect of rehybridization of the bonds of the ring atoms should raise the ester frequency in I-5 to 1757 cm⁻¹ appears unfounded in fact. It seems more reasonable to assign the band which centers at 1730 cm⁻¹ in I-5 and at 1733 cm⁻¹ in II-5 to the ester absorption. Moreover, the general contour of the 1757 cm⁻¹ band, the relative intensities of the two bands, and the splitting of the 1733 cm⁻¹ band of II-5 in TCE (see below) all

²² R. N. Jones and C. Sandorfy, *Techniques of Organic Chemistry* (Edited by A. Weissberger) Vol. IX, p. 453. Interscience (1956).

Compound	State	^y 0≔0 ester	ν _{C=0} ketone
11-5	liq.	1733 s	1754 s
	TČE	1738 s, 1728 sh	1755 s
	CH ₃ CN	1726 s, 1718 sh	1746 s
	CHCl ³	1725 s	1747 s
۹ II-6	liq.	~1736 sh, ~1721 sh,	1715 s
	TĊE	∼1741 sh, ~1730 sh,	1719 s
	CCl4	\sim 1740 sh, \sim 1730 sh,	1719 s
	CH ₈ CN	∼1733 sh, ~1720 sh,	1711 s
	CHCl ₃	\sim 1722 sh,	1710 s
II-7	liq.	1738 s	1710 vs
	TĊE	1740 s	1711 vs
II-8	liq.	1738 s	1710 vs
	TĊE	17 41 s	1713 vs
II-9	liq.	1737 s	1710 vs
	TĊE	1741 s	1712 vs
II-10	liq.	1737 s	1709 vs
	TCE	1741 s	1711 vs
II-12	liq.	1741 s	1714 vs
	TĊE	1741 s	1714 vs
II-15	liq.	1740 s	1713 vs
	TCE	1740 s	1714 vs
C-CH ₈ deriv.	liq.	1742 s-m	1715 vs
of IV	TCE	1739 s–m	1714 vs

TABLE 5. INFRARED ABSORPTION DATA FOR NON-ENOLIZABLE eta-ketoesters *

^a See Table 4 footnotes.

^b This compound shows a complex carbonyl envelope which was not resolved in any of the solvents listed.

serve to support the assignments adopted in this paper.²³ Finally, it may be noted that the frequency assignments made here successfully explain the apparent anomalies in band intensities of the various derivatives of I-5 reported in the earlier work.¹⁷

To facilitate comparison of the absorption characteristics of a given vibrational mode within the systematically varied series, the discussion which follows will deal first with the ketone absorptions, secondly, with the (non-conjugated) ester absorptions, and finally with the absorption bands of the chelated enolic species.

- ²⁸ An additional problem with the earlier assignment of the 1725 cm⁻¹ (1730 cm⁻¹) band to the ketone absorption in I-5 lies with providing a rational explanation for the 20 cm⁻¹ decrease in frequency from that of the parent ketone. The explanation offered,¹⁷ that the raised ester frequency in some way reduces the ring strain and hence the ketone frequency, seems untenable in view of the facts cited above. The usual explanation for frequency shifts of two characteristic absorptions in *opposite* directions is that of vibrational coupling of two close-lying frequencies (Fermi resonance).²⁴ This explanation seems unlikely for the case at hand, however, since the pair of bands shows the normal shifts in frequency with solvent polarity change (Table 4)²⁶ and because of the splitting of the 1733 cm⁻¹ band of II-5 in TCE, which behavior parallels completely that observed for the ester bands in β -ketoesters of structure I.
- ³⁴ Ref. 22, p. 495 and 480.
- ³⁶ L. J. Bellamy and R. L. Williams, *Trans. Faraday Soc.* 55, 14 (1959); R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Canad. J. Chem.* 37, 2007 (1959).



FIG. 2. Infrared spectra of enolizable β -ketoesters in 6 μ region. Band 1: $\nu_{0-0 \text{ oter}}$; band 2: $\nu_{0-0 \text{ ketone}}$; band 3: $\nu_{C=0 \text{ conj. chel.}}$; band 4: $\nu_{C=0 \text{ conj. chel.}}$. Curves a and b: solutions in TCE; curve c: liquid film.



FIG. 3. Infrared spectra of non-enolizable β -ketoesters in 6 μ region. Band 1: $\nu_{0=0 \text{ enter}}$; band 2: $\nu_{0=0 \text{ ketone}}$. Curve a: solution in TCE; curve c: liquid film.

Ketone C-O absorption in I and II

In general, the ketone C—O absorptions in the β -ketoesters (I and II) appear as quite sharp, intense bands of good symmetry as can be seen in Fig. 2 and 3 (band number 2). Insofar as they have been examined in different solvents (cf. Tables 4 and 5), these bands retain their characteristic shapes and relative intensities and show only the usual frequency shifts associated with such solvent changes;²⁶ no splitting of the

State	n	v _{cyclanone}	$\frac{\Delta \nu_{\rm I}}{(\nu_{\rm I} - \nu_{\rm cyclanope})}$	$\frac{\Delta v_{II}}{(v_{II} - v_{cyclanone})}$
liq.	5	1747	+10	+7
TČE		1748	·+9	+7
liq.	6	1714	+6(?)*	+1
TCE		1720	1	-1
liq.	7	1703	+5	+7
TCE		1707	- ⊢4	+4
liq.	8	1701	+8	-+9
TCE		1704	+6	- -9
liq:	9	1701	- + 8	+9
TCE		1703	- ⊢ 8	+9
liq.	10	1702	+9	- ¦-7
TCE		1704	+-7	+7
liq.	11	1709	+5	+4
TCE		1709	+5	+3
liq.	12	1709	+5	+5
TCE		1709	+5	+5
liq.	15	1712	+1	+1
TCE		1712	+2	+ 2

TABLE 6. KETONE FREQUENCY SHIFTS IN β -KETOESTERS I AND II ^a

^a Frequencies in cm⁻¹.

^b Shift only apparent. See text.

ketone band has been observed for any of the cyclic compounds studied. This behaviour is not duplicated in the ester bands; in all cases, the latter band is broader than that of the ketone and shows marked variation in contour and apparent intensity with structural change and with change in solvent (see below).

It is of interest to compare the ketone frequencies of the β -ketoesters with those of the parent ketones since it might reasonably be expected that such compounds would show frequency shifts indicative of conformational preferences such as have been observed for 2-halocyclanones.^{28–29} A tabulation of pertinent data is shown in Table 6 for the β -ketoesters of types I and II and the corresponding cyclanones. The band positions are given for the pure liquids and for solutions in TCE. The frequency shifts observed ($\Delta \nu$) for both the enolizable β -ketoesters, I, and their C-methyl derivatives, II, parallel one another rather closely in the series and show a maximum of

^{27a} N. L. Allinger and J. Allinger, J. Amer. Chem. Soc. 80, 5476 (1958).

- ^c J. Allinger and N. L. Allinger, J. Amer. Chem. Soc. 81, 5736 (1959).
- ²⁸ F. V. Brutcher, T. Roberts, S. J. Barr and N. Pearson, J. Amer. Chem. Soc. 81, 4915 (1959).
- ²⁹ N. J. Leonard and F. H. Owens, J. Amer. Chem. Soc. 80, 6036 (1958).

²⁶ E. J. Corey, J. Amer. Chem. Soc. 75, 2301, 3297, 4832 (1953); 76, 175 (1954).

^b J. Allinger and N. L. Allinger, Tetrahedron 2, 64 (1958).

7-10 cm⁻¹ for the five-membered ring compound and the medium ring compounds (n = 5, 8, 9, 10). While these shifts are rather small it is noteworthy that they are of the same order of magnitude and show the same trend as those reported for the corresponding α -bromocyclanones.^{29,30} These departures from the normal values suggest that in the five-, eight-, nine- and ten-membered ring derivatives the major conformation is one in which the carbethoxy group and the ketone function maintain a *syn-skew* (*syn-clinal*) relationship while in the six-membered and the 15-membered ring compounds, the absence of a frequency shift implies a high proportion of the axial conformer. The 7-, 11-, and 12-membered ring derivatives which show intermediate values of $\Delta \nu$ presumably possess conformations of intermediate geometry.

The frequency shifts in the five-membered ring β -ketoesters are relatively high $(\Delta \nu = +7 \text{ to } +10 \text{ cm}^{-1})$ for this series and correspond closely to that reported by Brutcher *et al.*²⁸ for 2-bromocyclopentanone ($\Delta \nu = 8 \text{ cm}^{-1}$), a fact which suggests that in I-5 and II-5 the preferred conformation is one in which the carbethoxy group adopts the "quasi-axial" position in the half-chair conformation of cyclopentanone.²⁸ This suggestion gains support from the frequencies reported by Leonard *et al.*¹⁷ for 2,5-dicarbethoxycyclopentanone (V). The latter molecule (in its keto form) shows a strong band at 1763 cm⁻¹ (ketone) and a very strong band at 1736 cm⁻¹ (ester). If the molecule assumes a half-chair conformation with the two carbethoxy groups in quasi-axial positions then the effect on the normal ketone frequency should be twice that observed for one carbethoxy group (2 × 10 cm⁻¹) in good agreement with the value reported ($\Delta \nu = +19 \text{ cm}^{-1}$).



The strong, normal carbonyl frequency found for the six-membered ring β -ketoesters I-6 and II-6 suggests that the major conformation in these molecules is one in which the carbethoxy group is axially disposed. The shift of +6 cm⁻¹ observed for I-6 in the liquid state when compared with the ketone itself is only an apparent shift as shown by the identity of these frequencies in TCE. A reasonable explanation for the apparent shift is found in the fact that because of the high enol content the molecules of the keto tautomer of I-6 are actually in solution in the relatively non-polar chelated enol. This would give the same effect as a change to a non-polar solvent and would shift the frequency upward by a small amount.

The spectrum of II-6 in the 6 μ region is unusual in that it consists of an unresolved envelope of absorption bands (Fig. 3), which peaks at the normal ketone frequency

1636

³⁰ There is little information available concerning the magnitude of the effect of dipole interaction between ketone and ester functions; however, it has been observed that 20-keto-21-acetoxysteroids show abnormally high frequencies in both the ketone and ester carbonyl vibrations and this has been attributed to dipolar field effects. (Ref. 22, p. 480.) These shifts amount to +23 cm⁻¹ for the ketone and +18 cm⁻¹ for the ester frequency and are of the same order of magnitude as those observed in the equatorial bromo derivatives of cyclohexanone (+16 to +20 cm⁻¹).³⁶

but has poorly defined shoulders at higher frequencies. Attempts to resolve these bands by solvent variation were unsuccessful (Table 5); the envelope retained its general characteristics through the solvent range noted in the Table. The failure of this envelope to resolve implies that the component bands are very closely spaced and suggests that this system probably does exist as a mixture of equatorial and axial conformers, the composition of which is insensitive to the solvent change imposed.27c Recently, Eliel et al.³¹ have reported conformational equilibrium studies for the carbethoxy group which lead to the conclusion that the carbethoxy group is somewhat smaller than the methyl group by a free energy difference of 0.6 kcal/m. In the compound 11-6, then, this suggests that, by steric factors alone, the conformation in which the carbethoxy group adopts the axial position would be favoured by a ratio of 3:1. Dipole interactions between the ketone function and the carbethoxy group might be expected to further destabilize the equatorial conformer relative to the axial. These considerations accord with the very strong absorption component of the envelope at the normal 1715 cm⁻¹ frequency (liq. film) but the lack of resolution of the envelope into normal ketone (1715 cm⁻¹) and ester (1736 cm⁻¹) frequency bands implies the presence of some equatorial conformer.



Ester C=O absorptions in I and II

The enolizable β -ketoesters I-6 through I-12 and I-15 exhibit relatively strong, somewhat broad, and often unsymmetric bands at 1740–1745 cm⁻¹ which are associated with the ester C—O stretching mode (see Table 4 and Fig. 2). If the value of 1736 cm⁻¹ reported for 4-carbethoxycyclohexanone¹⁷ is regarded as a normal ester frequency for the cyclic compounds then it appears that the center of the ester band is displaced upward somewhat (4–10 cm⁻¹) and this shift roughly corresponds to that of the ketone bands noted earlier. Of greater interest, however, are the changes in contour and intensity of the ester bands with structural and solvent changes—changes which suggest that they are envelopes containing at least two bands which can reasonably be attributed to conformational and/or rotational isomers.

In liquid films, the carbonyl stretching bands of the ketone and the ester functions of the β -ketoesters of type I are well separated and show interesting variations in relative intensity throughout the series. Judged by relative height on the percent absorption scale, the β -ketoesters fall into three groups: those in which Int._{ketone} > Int._{ester} (I-6, I-8, I-12 and I-15); those in which Int._{ester} > Int._{ketone} (I-5, I-7, and I-10); and those in which Int._{ketone} \cong Int._{ester} (I-9, I-11). Representative examples of each of these groups are included in Fig. 2 (I-10c, I-11c, I-12c). In fact, as would be expected from reported integrated intensities for ester and ketone bands,³² the ester absorption bands, in all cases, have a greater total intensity since they are always broader than the ketone bands and their greater breadth is especially pronounced in those cases in which the apparent intensities are reversed. The corresponding spectra

⁸¹ E. L. Eliel, H. Haubenstock and R. V. Acharya, J. Amer. Chem. Soc. 83, 2351 (1961).

³² Ref. 22, p. 465.

in TCE show in all cases except that of I-5, a relative decrease in the height of the ester band, accompanied by a broadening of the band and partial resolution (Fig. 2). This effect is especially noticeable in the compounds I-8 through I-11 in which the single band characteristic of the liquid film is split into its higher and lower frequency components (see Table 4 and Fig. 2). Since a corresponding broadening and splitting of the ketone band is not observed under these conditions, this has the effect of making the apparent ester intensity less than that of the ketone intensity for all the β -ketoesters examined except I-5.³³

The five-membered ring β -ketoester deserves special mention with respect to the points discussed above. It has already been noted that the ketone absorption band (1757 cm⁻¹) is displaced to a higher frequency relative to the simple ketone itself (1747 cm⁻¹). The ester carbonyl absorption at 1730 cm⁻¹ (liq. and TCE) is a very strong band of good symmetry, more intense and broader than the ketone band (Fig. 2). This pattern of relative intensities and symmetry persists in the spectrum of I-5 with solvent change (Table 4); no appreciable broadening, splitting, or diminution of apparent intensity occurs in this compound in contrast to the other β -ketoesters of type I. The frequency of the ester absorption, 1730 cm⁻¹, as pointed out earlier, is "normal", or even somewhat low. At any rate, it is certainly not displaced to an appreciably higher frequency by interaction with the ring carbonyl as might have been expected from the shift in the ketone band and by analogy to the 20-keto-21-acetoxysteroids.^{21,34}

In the non-enolizable β -ketoesters of type II, the ester carbonyl bands are diminished in intensity in comparison with the parent β -ketoesters and appear as poorly resolved peaks or shoulders on the very strong ketone bands which, in turn, appear to be less symmetrical than in the parent β -ketoesters (Fig. 3). The positions of the ester bands in II-6 through II-12 are generally displaced downward a bit in frequency from those found for the enolizable compounds to values that might be considered normal

³³ One might have expected that a similar band broadening and diminution of apparent intensity would have been observed for the ketone band also, since if the two bands of the ester envelope are indeed the result of conformational differences, a corresponding pair of bands should be detectable in the ketone absorption region. While no such change is evident by visual inspection of the bands, it may be that a more rigorous quantitative study would reveal these changes. The general intense absorption in the 1760–1700 cm⁻¹ region and the quite appreciable overlap of the ester and ketone bands may well be masking relatively weak bands of significantly different frequencies. Alternatively, the multiple bands observed in the ester region could simply be the result of rotational possibilities about the C—C bond of the ring-ester junction, i.e.

³⁴ One difficulty in assessing the magnitude of this effect lies with the selection of a "normal" value for a carbethoxy group attached to a cyclopentanone ring. Although there is good evidence that in simple cyclopentanones the ring assumes a half-chair conformation²⁸ there is no assurance that this is the case for monosubstituted cyclopentane derivatives and, indeed, it likely is not [cf. E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 251. McGraw-Hill, New York (1962)]. Whether a difference in ring conformation would affect the carbonyl frequency of a substituent ester group does not appear to be known, but the use of the 1740 cm⁻¹ frequency found for carbethoxy-cyclopentane as a "normal" value to be applied to cyclopentanone derivatives is, at least, open to question.

for esters of this type (1735–1740 cm⁻¹ in TCE).) With the exception of the five-membered ring compound, II-5, the C-methylated β -ketoesters show no striking differences when examined as liquid films and in TCE solution. The non-resolvability of the broad band of II-6 has been remarked earlier.

In TCE and acetonitrile, the unsymmetrical 1733 cm^{-1} ester peak of the liquid II-5 splits in a manner which parallels the behavior of the enolizable compounds I-8 through I-11. This splitting is particularly marked in TCE solution, the two components appearing at 1738 cm^{-1} and 1728 cm^{-1} (Fig. 3). Since this splitting is not duplicated in the ketone band (in which masking by other absorption is not likely) it seems probable that the two ester bands are to be accounted for in terms of rotational isomerism about the C—C bond of the ring and the ester function rather than in terms of conformational isomerism.

Enol	^v chel conj C=0	$\Delta \nu$ °	ν _{conj} C=C
I-5	1663	-67	1621
I-6	1655	-87	1615
I-7	1641	99	1611
I-8	1646		1609
I-9	1643	-102	1608
I-10	1642	102	1600
I-11	1644	-103	1601
I-12	1645	- 98	1604
I-15	1643	-101	1608
IV	1644	- 93	1609
III	1650	-90	1616

TABLE 7. INFRARED ABSORPTION BANDS OF CHELATED ENOLS IN TCE SOLUTION⁴

* Frequencies in cm⁻¹.

 $\delta \Delta v = v_{\text{chel conj } C=0} - v_{\text{unconj ester } C=0}$

Absorption bands of the chelated enols

Each of the enolizable β -ketoesters examined shows the pair of bands characteristic of the chelated enol in the region 1665–1600 cm⁻¹. These bands are best studied in dilute TCE solutions of the ketoesters since this solvent serves not only to enhance the enol content of some of the more weakly enolic compounds but also to sharpen the bands. It is of interest to note once more the relative indifference to solvent polarity of the band positions of the chelates which was remarked earlier in the ultraviolet studies (cf. Table 4). It may also be re-emphasized that the response to a solvent such as TCE in terms of enol content is small with I-12, I-15 and the acyclic compounds (III and IV); in those cases, it was necessary to employ more concentrated solutions of the β -ketoesters in order to obtain sharp peaks.

For convenience of reference, the positions of the chelate bands in TCE solution are shown in Table 7. The higher frequency band, assigned to the chelated, conjugated ester C=O stretching mode^{16,17} appears in the range 1665–1640 cm⁻¹, displaced some 70–100 cm⁻¹ from the ester frequency of the corresponding unconjugated β -keto-ester. The lower frequency band, associated with the conjugated C=C stretch,¹⁷ appears as a weaker band in the range 1620–1600 cm⁻¹.

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The changes in frequencies of these two bands within the series are small, but nonetheless real, and offer some insight into the nature of the responsible vibrations and the changes in structure of the chelate system through the series. Attention is first directed to the higher frequency band and its corresponding displacement from the unconjugated ester frequency ($\Delta \nu$). This band appears at appreciably higher frequencies for the five- and six-membered ring compounds (1663 cm⁻¹ and 1655 cm⁻¹) and then falls by 10–20 cm⁻¹ to a fairly constant frequency range for the higher homologs (~1640–1645 cm⁻¹). The acyclic derivatives (III and IV) show behavior which roughly parallels their cyclic counterparts. Finally, within the pair, I-5 and I-6, the frequency of this band is significantly higher in I-5 and the corresponding displacement of the ester band ($\Delta \nu$) attributed to the chelated system of conjugation is 20 cm⁻¹ less.⁻

The second band of the chelated enolic species in the $1620-1600 \text{ cm}^{-1}$ region shows a more regular pattern of frequency change in the series. In TCE solutions, this band shows an unmistakable trend to lower frequencies with increasing ring size until it reaches a minimum value with the 10- and 11-membered ring compounds; thereafter, it appears to increase again and the large ring compound, I-15, shows complete correspondence with its open chain analog, IV.³⁵

A rationalization of these trends in the positions of the characteristic bands of the chelated enols rests, first, on recognition of the fact that although it is convenient to classify these absorptions as arising from stretching motions of the C—O and C—C bonds, in reality, these motions are not localized in these bonds but are molecular vibrations—specifically, vibrations characteristic of the six atom, conjugate-chelate system, VI.



Changes in the frequencies of these characteristic vibrations imply changes in the degree of electron delocalization in the chelate systems; that is to say, the more effective the electron delocalization in the chelated, conjugated system, the "looser" the multiple bonds become and this loosening is reflected in a decrease in the characteristic frequencies. Following this line of reasoning, one concludes that structural effects in the ring systems in the series of enol chelates are acting to produce increasingly greater electron delocalization as the ring size changes up to ten members.

The relative stabilities of chelates of this sort are generally attributed to the degree of effective bridging of the hydrogen bond, which, in turn, depends on the $O \cdots O$ distances.³⁶⁻³⁸ If the trend in frequencies in the cyclic enol series is indeed a reflection

³⁵ This trend in v₀₌₀ is strongly reminiscent of the parallel trend in v₀₌₀ of the corresponding ketones which has been rationalized in terms of the hybridization of the carbonyl group's bonds induced by small angle distortions in the rings. Cf. W. M. Schubert and W. A. Sweeney, J. Amer. Chem. Soc. 77, 4172 (1955) and P. D. Bartlett and M. Stiles, *Ibid.* 77, 2804 (1955).

³⁰ G. C. Pimentel and A. L. McClellan, The Hydrogen Bond p. 85 ff. Freeman, San Francisco (1960).

⁸⁷ L. J. Bellamy, The Infrared Spectra of Complex Molecules p. 98. Methuen, London (1958).

³⁶ Unfortunately, the best measure of this effect, the position of the chelated OH absorption in the infrared is not applicable here since this band cannot be recognized in these compounds.

of the effectiveness of H-bonding, then one is dealing with a series in which the stability of the H-bonded chelate increases with increasing size as a result of decreasing $O \cdots O$ distance.

This requirement of decreasing $O \cdots O$ distance can be accommodated by a simple treatment of the geometry of the chelated system, VI, as it is affected by angle changes at the olefinic carbons. In the five-membered ring enol, the internal ring angles, β , are constrained to a value considerably less than the normal 120° required for pure sp² hybridization. Presumably, this constraint is accommodated by rehybridization at the olefinic carbon atoms so that the bonds directed toward the ring atoms have more "p" character. If one assumes that the effect on the pi bond itself is negligible, then it follows that the bonds directed toward the OH and the COOR groups will have more "s" character and the external angles, α , will take on values greater than 120°. This compensating spreading of the angles, α , will increase the O · · · O distance, decrease the effectiveness of H-bonding, and, ultimately be manifested in a decrease in electron delocalization as gauged by the frequencies associated with the system. If the six-membered ring system and its frequencies are adopted as "normal" for this series, then the fall-off in frequencies observed in the series requires that for rings larger than six, the internal angles, β , are spread somewhat by steric pressures in the ring to take on values greater than 120° and bond rehybridization in these systems will operate in a manner to decrease α , bring the oxygens closer together, and permit more effective interaction through the H-bridge.³⁹⁻⁴⁰ It is reasonable that the *cis* enols of the acylic compounds III and IV would show this same behavior and that the frequency decreases in IV would be more pronounced since greater steric pressures are acting to spread the angles, β . The *cis* enol of acetoacetic ester, on the other hand, shows appreciably higher frequencies—behavior which again seems consistent with the general picture. Finally, it may be noted that Baeyer strain is an important component of the total strain energy in the medium ring systems; the average bond angle in cyclodecane, for example, shows a positive deviation from the value characteristic of straight chain alkanes.⁴¹

As a corollary of this picture of increasing chelate stability through the series I-5 to I-10, I-11, differences in the acidities of the enols themselves may be anticipated. Thus, the five-membered ring enol should be the strongest acid of all since the effectiveness of H-bonding is at a minimum in this system while the acidities of the enolic species of I-10 and I-11 should be correspondingly low. That this expectation is borne out is demonstrated in the following paper.⁴²

- ³⁹ Basically, this argument is the same one which was used to rationalize the trend in $\nu_{c=0}$ in the cyclanones. Ref. 35.
- ⁴⁰ Although bond angle values for cycloalkenes are not available, some evidence that the angles do vary in the manner described is available from the frequency change in the C—H stretching vibrations of the vinyl hydrogens. For example, K. B. Wiberg and B. J. Nist, J. Amer. Chem. Soc. 83) 1226 (1961), have reported v_{0-0-H} for the series cyclopentene, cyclohexene, cycloheptene, and (cis) cyclooctene as 3061, 3024, 3020 and 3016 cm⁻¹. The regular decrease in frequency implies a weakening of the C—H bond and corresponds to decreasing "s" character.

⁴⁹ Additional evidence for the changing geometry and chelate stability through the series of enols is found in the N.M.R. spectra of these compounds. These results will be presented in a forthcoming publication.

⁴¹ Ref. 3, p. 206.

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EXPERIMENTAL^{4*}

Materials. The five- and six-membered cyclic β -ketoesters (I-5, I-6) were prepared by standard methods (see Table 1). Ethyl α -ethylacetoacetate (III) was prepared from ethyl acetoacetate and ethyl iodide by standard alkylation procedure in ethanolic solution with sodium ethoxide. Final purification was accomplished by fractionation in a spinning band column. Ethyl 2-(n-hexyl)-3-ketodecanoate (IV) was synthesized by a Claisen condensation of ethyl octanoate in xylene promoted by sodium hydride by the general procedure described elsewhere.⁴⁴ The product had physical properties which corresponded closely to those reported by others.45 Cycloheptanone, cyclooctanone and cyclopentadecanone were commercial products and were rectified prior to use to a purity of 99% or better. Cyclic ketones of ring size 9-12 were prepared by the acyloin synthesis followed by zinc dust-acid reduction.46-49 The ketones so prepared were purified by distillation and over their semicarbazones to purities of no less than 95%. The α,ω -dicarboxylic acid methyl esters required in the acyloin syntheses were either carefully purified commercial products or were prepared from the commercially available acids by esterification with methanol by the method of Clinton and Laskowski.⁵⁰ In the synthetic sequences leading to the materials described above the purities of all starting materials and intermediates were routinely checked by g.l.p.c. and were uniformly high (>95%).

2-Carbethoxycyclanones. Diethyl carbonate-sodium hydride method

General procedure. A three-necked flask was fitted with a mercury-sealed stirrer, a pressurecompensating dropping funnel and an air condenser equipped with a T-tube for the introduction of dry nitrogen into the apparatus and the entire system was swept with dry nitrogen for 1 hr prior to the addition of reagents. Approximately 350 ml diethyl carbonate (Matheson, Coleman and Bell) was distilled from a few grams of sodium hydride directly into the reaction flask containing 0.4 mole sodium hydride in the form of a 50% dispersion in mineral oil (Metal Hydrides Co.). All of these operations were performed under a protective blanket of dry nitrogen. The appropriate ketone (0.2 mole), dissolved in a small amount of dry diethyl carbonate or xylene, was added dropwise to the stirring sodium hydride-ethyl carbonate mixture over a period of 2-3 hr. Occasionally, 1-2 ml absolute ethanol was required to initiate the reaction. The nitrogen flow was stopped and the progress of the reaction was followed by observation of the evolution of hydrogen in a gas-bubbler attached to the T-tube. The entire reaction was conducted at room temp. Stirring was continued until no further gas evolution was observed. (Usually this required time intervals of 1 to 4 hr; however, in the carbethoxylation of cyclopentadecanone, hydrogen evolution did not cease until the reaction mixture had stood overnight.) During this time a thick slurry of sodium enolate usually formed. The reaction mixture was poured into an ice-cold mixture of ether, water and a slight excess of acetic acid. The organic layer was separated, washed with ice-cold 10% sodium carbonate solution to neutrality and dried over anhydrous sodium sulphate. After a forerun of solvent and diethyl carbonate, the product remained as a high-boiling residue which was purified by repeated vacuum distillation to remove contaminating, unreacted ketone. Yields and properties of the 2-carbethoxycyclanones prepared by this method are recorded in Table 1.⁵¹ For the higher boiling β -ketoesters (I-11, I-12 and I-15) it was found advisable to remove the mineral oil from the sodium hydride dispersion by washing (under

- ⁴³ M.p. are corrected. Analyses by Schwarzkopf Microanalytical Lab., Woodside, N.Y., Weiler and Strauss Microanalytical Lab., Oxford, England, and Clark Microanalytical Lab., Urbana, Ill.
- 44 Manual of Metal Hydrides p. 4. Metal Hydrides Co., Beverly, Mass.
- ⁴⁵ R. H. Briese and S. M. McElvain, J. Amer. Chem. Soc. 55, 1697 (1933).
- 46 V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, Helv. Chim. Acta 30, 1741 (1947).
- 47 M. Stoll and J. Hulstkamp, Helv. Chim. Acta 30, 1815 (1947).
- 49 Organic Syntheses Vol. 36, pp. 14, 17. John Wiley, N.Y. (1956).
- 49 H. C. Brown and M. Borkowski, J. Amer. Chem. Soc. 74, 1894 (1952).
- ⁵⁰ R. O. Clinton and S. C. Laskowski, J. Amer. Chem. Soc. 70, 3135 (1948).
- ⁵¹ It should be noted that in our experience this method has proved definitely inferior to the usual method for the preparation of I-6 (Table 1, Method B). When I-6 was prepared in the manner described above, it was contaminated by quite appreciable amounts of what seemed to be the self-condensation product of cyclohexanone. It appears that the diethyl carbonate-sodium hydride method is best suited to ketones of low acidity coupled with low electrophilicity.

nitrogen) with inert solvents prior to the introduction of the other reagents. In this way, contamination of the product by front ends of the mineral oil can be avoided.

Methylation of β -ketoesters

General procedure. While preparative methylation of the more acidic β -ketoesters, I-5 through I-8 and III, could be accomplished in reasonable yield by the conventional method of using ethanolic sodium ethoxide and excess methyl iodide, the following procedure was required for the less acidic β -ketoesters and is generally preferable for all the β -ketoesters of this type.

Into a three-necked flask fitted with a condenser and nitrogen inlet and equipped for magnetic stirring, was introduced a quantity of 50% sodium hydride dispersion in mineral oil equivalent to the amount of β -ketoester to be methylated. The dispersion was washed free of mineral oil and overlaid with dry benzene. The appropriate β -ketoester was introduced into the reaction flask and the mixture

Company	Compound Formula		lc'd	For	ind
Compound	ronnula	%C	%Н	%С	%Н
11-7	C ₁₁ H ₁₈ O ₃	66.6	9.2	66.4	9-3
II-8	C12H20O3	67-9	9.5	67.8	9.7
II-9	C13H23O3	69·0	9.8	69.4	9.6
II-10	C14H24O3	70-0	10-1	70-2	10·0
II-11	C15H26O3	70.8	10.3	71.1	10.5
II-12	$C_{16}H_{28}O_{3}$	71.6	10-5	71.9	10.7
II-15	C19H34O3	73.5	I1·0	73.7	11-2
C-CH ₃ deriv. of IV	$C_{19}H_{36}O_3$	73·0	11.6	73·0	11.8

TABLE 8. C-METHYLATED β -ketoesters

was stirred 1 to 2 hr to complete formation of the sodium salt. A 7- to 10-fold excess of methyl iodide was added and the reaction mixture allowed to stir at room temp 20-24 hr after which time it was poured into dilute acetic acid and worked up in the usual manner. The methylated products obtained by this procedure usually still contained small amounts of unreacted β -ketoesters and were further purified for spectral studies and for analyses by g.l.p.c. "trap-out" techniques. This process furnished C-methylated derivatives of at least 99% purity. The properties of the C-methyl derivatives are shown in Tables 3 and 8.

Decarboxylation of methylated β -ketoesters

General procedure. Decarboxylation of the 2-methyl-2-carbethoxycyclanones (II) and of the C-methyl derivative of IV was accomplished by refluxing the methyl derivative in 6 N hydrochloric or sulphuric acid for 70 to 120 hr periods. (In some cases, a water-ethanol solvent system was required to effect solution). The methylated ketones, isolated after standard work-up procedures, were separated from traces of contaminating C-methylated β -ketoesters by g.l.p.c. trapping. The ketones were converted to their semicarbazones for characterization and analysis. See Table 9.

TABLE 9. SEMICARBAZONES OF 2-METHYLCYCLANONES

Consideration of	Ma Farmula		Calc'd				Found	
Semicarbazone oi	м.р.	Formula	%C	%н	%N	%C	%н	%N
2-Methylcyclooctanone	140.5-141.1	CieHieON.	60.9	9.7	21.2	61.3	9.6	21.2
2-Methylcyclononanone	144-2-145-0	C,H.ON.	62.5	10.0	19.8	61-9	10.3	19-9
2-Methylcyclodecanone	180.4-181.2	C,H,ON,	64.0	10.3	18.7	64·0	10.3	18.8
2-Methylcycloundecanone	176-8-177-6	C, H, ON,	65-2	10.5	17.6	65·0	10-1	17.5
2-Methylcyclododecanone	196.0-197.0	C.H.ON.	66-4	10.7	16.6	66.2	10.5	16.6
2-Methylcyclopentadecanone	143.7-145.2	C ₁₇ H ₃₃ ON ₃	69-1	11.3	14.2	69-2	11.2	14.3
7-Methyl-8-ketopentadecanone *		C ₁₆ H ₃₂ O	79·9	13.4		80.0	13.6	

^a Analysis is for the ketone since no solid derivative could be prepared.

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Gas-liquid-partition-chromatography. The routine use of g.l.p.c. for purity checks and for the isolation of mixture components in this investigation necessitated the development of some special columns. The enolizable β -ketoesters showed peculiarities on g.l.p.c. analysis on commonly used packings which suggested that they were undergoing thermal decomposition at temperatures of 200° and over; extraneous peaks appeared (especially, that of the corresponding ketone), the recorder patterns showed wide variation with flow rate, sample size and temperature, and the effluent gases revealed the presence of carbon dioxide. It was found that such behavior could largely be avoided by the use of packings of low substrate concentration on glass Microbeads (Microbeads, Inc., Toledo, Ohio).⁴³ It is noteworthy that this difficulty seemed limited to the enolizable β -ketoesters; the corresponding C-methylated derivatives showed no marked tendency to decompose and gave clean, symmetrical peaks with a variety of common column materials. The columns and conditions most commonly used in this work are described below.

Column	Packing	Length	Recommended for
1	10% Reoplex-400 on Fluoropak 80	2-5 m	Cyclanones of ring size 5–11. Temp. 150–200°.
2	0.125% DC silicone grease on Microbeads	1·7 m	Enolizable β -ketoesters. Temp. 125–170°.
3	1.0% Reoplex-400 on 4:1 Microbead- Fluoropak mixture	2·5 m	Non-enolizable β -ketoesters. Temp. 175–225°.

Analyses and isolations were carried out in a Perkin-Elmer Model 154C Vapor Fractometer. The injection block was fitted with an auxiliary 300 watt heater; ordinarily, 85-90 volts was applied to the heater to assure vaporization of high boiling samples. Helium was the carrier gas in all cases.

Spectral measurements

Ultraviolet spectra. Spectra in the U.V. region were obtained with a Beckman Model DB instrument on solutions in spectro-grade solvents in matched 1 cm cells. The solutions of enolizable β -ketoesters were allowed to stand in the dark 7-8 days before measurements were made.

Infrared spectra. Spectra in the I.R. region were recorded on a Perkin-Elmer Model 21 instrument (sodium chloride prism, resolution 927, gain 6, minimal speed at peaks). The instrument was calibrated prior to each day's run with an indene-camphor-cyclohexanone standard in the 5.5-6.5 μ region.⁵³ Solutions were prepared with spectro-grade solvents. Solvent absorption was corrected for by a compensating wedge of the same solvent.

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- ⁵² The advantages of Microbead packings for high mol. wt. compounds have been pointed out by C. Hishta, J. P. Messerly and R. F. Reschke, *Analyt. Chem.* **32**, 1730 (1960).
- ⁵³ Iupac tables of wavenumbers for the calibration of infra-red spectrometers p. 680. Butterworths, Washington (1961).