Tetrahedron, 1966, Vol. 22, pp. 3557 to 3570. Pergamon Press Ltd. Printed in Northern Ireland

A KINETIC STUDY OF C- AND O-ALKYLATION OF SOME CYCLIC β-KETO ESTERS[1]

SARA JANE RHOADS and R. W. HASBROUCK
Department of Chemistry, University of Wyoming, Laramie, Wyoming

(*Received USA* 28 *March* 1966; *accepted for publication* 16 *May* 1966)

Abstract—The reactions of sodio-2-carbethoxycyclanones of 5, 6 and 8 ring members (I-5, I-6, I-8) with isopropyl iodide in dimethylsulfoxide (DMSO) have been studied kinetically at three temps. Three competing second order reactions occur: isopropylation at carbon, isopropylation at oxygen and propene formation. The total rate constants were dissected into individual rate constants by an independent measurement of propene formation and by GLC of the alkylation product mixtures. At 30°, the C/O ratios for I-5, I-6 and I-8 are 1·74, 1·34 and 7·72 respectively. Increasing temps favor O-alkylation in all cases since it has the higher enthalpy of activation of the two alkylation processes. Relative rates of C-alkylation at 30° for I-5:I-6:I-8 are 1·7:1:4·4 whereas for O-alkylation the relative rates are 1·3:1:0·8. The insensitivity of the O-alkylation process to structural change in the anion and the anomalous position of I-8 in the reaction series for O-alkylation are attributed to a coincidence of the experimental temperature and the isokinetic temp.

AMBIDENT anion reactions have received much attention in recent years and it is becoming increasingly apparent that a number of factors enter into the partitioning of reaction at the available sites.[2] Among these, steric and reactivity effects in the alkylating agent,[2a–d] the influence of the nature of the cation[2e–g] and of reaction heterogeneity,[2h] the contributions of free ions, ion-pairs and higher ionic aggregate species,[2i–k] and the unique, often overridingly important, role played by the solvent[2l–q] have been recognized and rationalized in a unifying manner through the extensive contributions of Kornblum and his students.[2a] One aspect of the problem that has received little attention, however, is that of structural effects in the anions themselves.[3]

---

[1] Abstracted in part from the Ph.D. dissertation of R. W. H., University of Wyoming, June (1964).

[2] [a] N. Kornblum, B. Taub and H. E. Ungnade, *J. Amer. Chem. Soc.* **76**, 3209 (1954); [b] N. Kornblum, R. A. Smiley, H. E. Ungnade, A. M. White, B. Taub and S. A. Herbert, *Ibid.* **77**, 5528 (1954); [c] N. Kornblum, L. Fishbein and R. A. Smiley, *Ibid.* **77**, 6261 (1955); [d] N. Kornblum and L. Fishbein, *Ibid.* **77**, 6266 (1955); [e] A. Brändström and I. Forsblad, *Acta Chem. Scand.* **11**, 914 (1957); [f] I. Forsblad, *Arkiv för Kemi* **15**, 403 (1960); [g] A. Chatterjee, D. Banerjee and S. Banerjee, *Tetrahedron Letters* 3851 (1965); [h] N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.* **81**, 705 (1959); [i] A. Brändström, *Arkiv för Kemi* **6**, 1955 (1953); **7**, 81 (1954); **11**, 567 (1957); **13**, 51 (1958); [j] D. Y. Curtin, R. J. Crawford and M. Wilhelm, *J. Amer. Chem. Soc.* **80**, 1391 (1958); [k] C. F. Hobbs, C. K. MacMillan, E. P. Papadopoulus and C. A. Vanderwerf, *Ibid.* **84**, 43 (1962); [l] H. D. Zook and T. J. Russo, *Ibid.* **82**, 1258 (1960); [m] H. E. Zaugg, B. W. Horrom and S. Borgwardt, *Ibid.* **82**, 2895 (1960); [n] H. E. Zaugg, *Ibid.* **82**, 2903 (1960); [o] G. Brieger and W. M. Pelletier, *Tetrahedron Letters* 3555 (1965); [p] N. Kornblum, P. J. Berrigan and W. J. LeNoble, *J. Amer. Chem. Soc.* **81**, 705 (1959); **85**, 1141 (1963); [q] N. Kornblum, R. Seltzer and P. Haberfield, *Ibid.* **85**, 1148 (1963); [r] R. C. Kerber, G. W. Urry and N. Kornblum, *Ibid.* **87**, 4520 (1965).

[3] Arguments based on steric considerations in the anions have been invoked in isolated examples to explain observed changes in alkylation product composition. Cf. [a] H. Rinderknecht, *J. Amer. Chem. Soc.* **73**, 5770 (1951); [b] N. Kornblum and R. Seltzer, *Ibid.* **83**, 3368 (1961); [c] A recent paper which reports on the effect of ring size on the C/O ratio in acylation of cyclic β-ketoesters is that of J. P. Ferris, C. F. Sullivan and B. G. Wright, *J. Org. Chem.* **29**, 87 (1964).

In view of the pronounced tendency of cyclic β-ketoesters of 5 and 6 ring members to undergo O-alkylation under conditions which lead to exclusive C-alkylation in their acyclic counterparts,[2e–g,4] the ambident anions of cyclic β-keto esters appear to offer a system especially well disposed to competitive alkylation studies and one equally well suited to an examination of the steric requirements in the anion component of these reactions through a systematic change in ring size.

In the present study, kinetic data are reported for the alkylations of the sodio-2-carbethoxycyclanones of 5, 6 and 8 ring members (I n) with isopropyl iodide in DMSO.[5] This choice of alkylating agent and solvent was dictated by the fact that the combination gives accurately measureable amounts of both products and by the goal of assessing the intrinsic nucleophilicities of the two alkylation sites insofar as it is possible in a solvent system. To this end, we have employed DMSO, an aprotic solvent of high dielectric, which, presumably, strongly solvates the sodium cation, but leaves the reactive sites of the anion relatively unencumbered.[2a,6,7]

The reaction

Under the reaction conditions, four products are detectable in the reaction mixture, the C-alkylation product (IIn) the primary O-alkylation product containing an α,β-unsaturated ester system (IIIn) the β,γ-unsaturated O-alkylation product (IVn) produced by isomerization of IIIn,[9] and propene, product of a concurrent elimination process. The alkylation products were isolated by GLC and their structures established by IR, UV and NMR spectra. The structurally significant data are assembled in Table 4 of the experimental section.[10] Noteworthy are the characteristic low intensity $n \rightarrow \pi^*$ absorption bands of the ketone functions in the UV and the typical ketone and ester bands in the IR for IIn.[11] The O-derivatives of the conjugated system (IIIn) are characterized by high intensity $\pi \rightarrow \pi^*$ absorption around 250 mμ in the UV and

---

[4a] W. von E. Doering and S. J. Rhoads, *J. Amer. Chem. Soc.* **73**, 3082 (1951); [b] S. J. Rhoads, R. D. Reynolds and R. Raulins, *Ibid.* **74**, 2889 (1952).

[5] The kinetic study was confined to these three ring systems when preliminary experiments showed that the C/O ratios were appreciably greater with the 7- and 10-membered ring systems (C/O ~ 15 for I-7 and ~32 for I-10 at room temp). Since extraction of meaningful activation parameters depends on the accuracy of the C/O ratio measurements, quantitative study for the present has been restricted to those cycles in which the competition is more evenly balanced.

[6] A. J. Parker, *Quart. Rev.* **16**, 163 (1962).

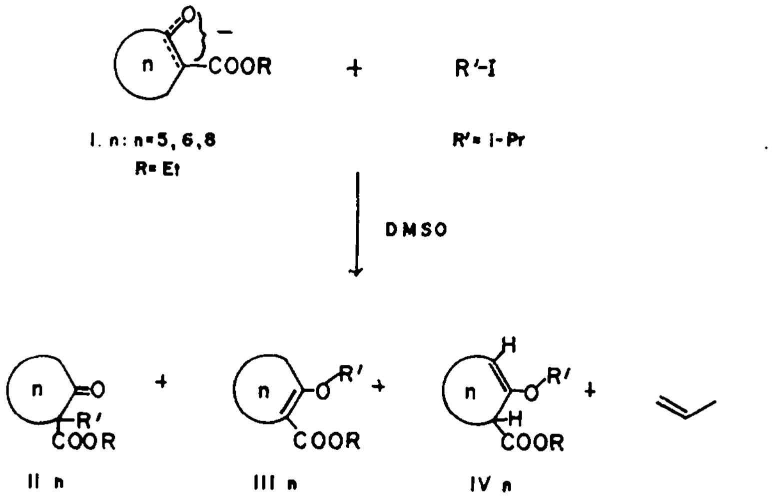
[7] It is not implied, however, that dissociation of ion-pairs is complete under these conditions, or even extensive. In dimethylsulfoxide solutions of the concentrations required for kinetic study, even simple electrolytes are appreciably associated;[8] with strongly chelated salts of the type employed in the present study, association of the counter ions must be rather extensive. We are presently engaged in conductance measurements of solutions of the sodium enolates in DMSO and other aprotic solvents in order to determine the relative importance of ionic and ion pair components in the alkylation reactions.

[8] P. G. Sears, G. R. Lester and L. R. Dawson, *J. Phys. Chem.* **60**, 1433 (1956).

[9] The amount of the β,γ-isomer found in the reaction mixture is a function of the time elapsed between completion of the reaction and workup. This facile $\alpha,\beta,\beta,\gamma$-isomerization of the O-derivatives is currently under investigation.

[10] Complete details and discussion of the spectra of these derivatives will be presented at a later date in connection with the related problem of $\alpha,\beta,\beta,\gamma$-isomerization.

[11] S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler and M. J. Urbigkit, *Tetrahedron* **19**, 1625 (1963).



strong ester and double bond absorption in the IR in accord with conjugated systems of this general structure.[12] The O-derivatives of the non-conjugated system (IVn) show no maximum in the 320–220 mμ region of the UV, typical absorption positions and intensities in the IR for isolated ester carbonyl and vinyl ether double bonds, and the presence of one vinyl proton and one α-proton in the NMR spectra.

The presence of the elimination product, propene, was established by GLC of the reaction mixture and by direct isolation and titration.

Rate studies

The general reaction scheme consists of three competing second order reactions characterized by the rate constants k_c, k_o and k_p for C-alkylation, O-alkylation and propene formation. (Eq. 1 where E denotes enolate ion and P denotes isopropyl iodide.)

$$E + P \left[\begin{array}{l} \xrightarrow{k_c} \text{C-alkylation product} + I^- \\ \xrightarrow{k_o} \text{O-alkylation products} + I^- \\ \xrightarrow{k_p} \text{propene} + EH + I^- \end{array} \right. \qquad (1)$$

The rate expression for the total reaction in terms of enolate ion consumption is given by

$$-d(E)/dt = k_c(E)(P) + k_o(E)(P) + k_p(E)(P) \qquad (2)$$

or

$$-d(E)/dt = k_T(E)(P) \qquad (3)$$

where

$$k_T = \text{total rate constant} = k_c + k_o + k_p \qquad (4)$$

The consumption of the basic species, E, was followed titrimetrically and the total rate constant, k_T, evaluated by a least squares treatment of the data. In order to extract the individual rate constants, k_p was evaluated by an independent determination, and the ratio k_c/k_o was determined by GLC analysis of the alkylation reaction mixture.

---

[12] S. J. Rhoads, R. W. Hasbrouck, C. Pryde, and R. W. Holder, *Tetrahedron Letters* 669 (1963).

Since

$$k_T = k_C + k_O + k_P$$

and

$$k_C/k_O = (C)/(O) \tag{5}$$

Where (C) and (O) represent the amounts of C- and O-alkylated products produced by competing second order processes at time t, it follows that

$$k_O = (k_T - k_P)/(C/O + 1) \tag{6}$$

and

$$k_C = k_T - k_P - k_O \tag{7}$$

The kinetic behavior of the alkylation and elimination reactions was established by evaluation of the total rate constant, k_T, at several initial iodide concentrations. In these runs, the initial enolate concentration was held constant (*ca.* 0·05 M) in order to avoid the complicating factor of change in mechanism (ionic *vs.* ion-pair) introduced by dilution[2f,13] and to maintain reaction homogeneity.[2h] Although all the kinetic runs carried out in this manner showed good second order behavior as judged by the linearity of *log (P)/(E) vs. t* plots through 70–80 percent reaction, it was found that the value of k_T decreased linearly with the mole fraction of iodide added (Tables 5 and 6, Experimental). The linearity of the decrease in rate constant suggested that the cause was one of a small change in medium produced by dilution of the highly polar DMSO solvent with the relatively non-polar isopropyl iodide.[2m,n,14] That this was indeed the case was established by replacing a portion of the iodide with an inert solvent. The data in Table 5 demonstrate that the inert additives, benzene and tetrahydrofuran, had the same effect on k_T as did equivalent amounts of isopropyl iodide. From experimental rate data for all the enolates studied and at all temperatures, it was observed that an average of one percent decrease in rate constant resulted for each one thousandth mole fraction of iodide used. The observed rate constants, k_T, then were corrected for this medium dilution factor by the empirical relationship

$$k_{T\,obs} = k_{T\,corr} - (0{\cdot}01\, k_{T\,corr} \times 1000\, N_P) \tag{8}$$

or

$$k_{T\,corr} = k_{T\,obs}/(1 - 10\, N_P) \tag{9}$$

where $k_{T\,corr.}$ is the rate constant for an infinitely dilute solution of isopropyl iodide in DMSO and N_P is the mole fraction of iodide used. The constancy of the values of $k_{T\,corr}$ and of the C/O ratios through a fourfold change in initial iodide concentration (see sample data, Table 6 and 7) confirm the second order nature of the three processes.

An independent titrimetric determination of the propene concentration in the reaction mixture as a function of time, carried out according to the general procedure of Hughes *et al.*[15] permitted the evaluation of k_P through the relationship

$$k_P/k_{T\,corr} = (C_3H_6)_t/[(E)_o - (E)_t] \tag{10}$$

---

[13] S. J. Rhoads and A. W. Decora, *Tetrahedron* **19**, 1645 (1963).

[14] S. Videquist, *Arkiv för Kemi* **9**, 475 (1956), has reported similar effects in the methylation of acetoacetic ester in alcoholic solutions.

[15] E. D. Hughes, C. K. Ingold, and U. G. Shapiro, *J. Chem. Soc.* 225 (1936).

where the quantity, $[(E)_0 - (E)_t]$, represents the concentration of enolate ion consumed in time t. Details of the procedure and a sample calculation are set forth in the experimental section of this paper.

The corrected total rate constants, $k_{T\ corr}$, together with the rate constants, k_p, and the C/O ratios were used to evaluate the alkylation rate constants, k_c and k_o by Eqs (6) and (7). The reactions of the three sodioenolates were studied at three temperatures over a range of 20° and the activation parameters evaluated in the usual way. These various quantities are collected in Tables 1 and 2. The uncertainties given for k_c and k_o represent the maximum errors in these rate constants arising from the combined uncertainties in $k_{T\ corr}$, k_p and the C/O ratio. The errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the reactions of alkylation and elimination are statistical errors assessed by the method of Purlee *et al.*[16]

TABLE 1. RATE DATA FOR THE REACTIONS OF SODIO-2-CARBETHOXYCYCLANONES WITH ISOPROPYL IODIDE IN DMSO AT THREE TEMPERATURES

Compound	Temp	C/O ratio[a]	$k_{T\ corr}{}^{a} \times 10^4$ (1/mole-sec)	$k_p{}^{a} \times 10^4$ (1/mole-sec)	$k_c{}^{b} \times 10^4$ (1/mole-sec)	$k_o{}^{b} \times 10^4$ (1/mole-sec)
I-5	20·0	1·88 ± 0·02	6·56 ± 0·06	0·72 ± 0·03	3·81 ± 0·09	2·03 ± 0·05
	30·0	1·74 ± 0·02	17·1 ± 0·6	2·70 ± 0·24	9·15 ± 0·62	5·25 ± 0·35
	40·0	1·66 ± 0·01	41·7 ± 0·6	9·60 ± 1·1	20·1 ± 1·3	12·0 ± 0·8
I-6	20·0	1·44 ± 0·01	5·12 ± 0·02	0·811 ± 0·09	2·43 ± 0·08	1·76 ± 0·06
	30·0	1·34 ± 0·01	12·0 ± 0·1	2·70 ± 0·19	5·33 ± 0·23	3·97 ± 0·16
	40·0	1·24 ± 0·01	28·2 ± 0·7	8·95 ± 0·28	10·6 ± 0·7	8·58 ± 0·53
I-8	20·0	9·56 ± 0·30	11·9 ± 0·1	2·85 ± 0·18	8·19 ± 0·33	0·857 ± 0·035
	30·0	7·72 ± 0·05	33·0 ± 0·7	6·80 ± 0·51	23·2 ± 1·2	3·01 ± 0·16
	40·0	6·02 ± 0·06	88·1 ± 2·6	17·4 ± 4·0	60·7 ± 6·2	10·0 ± 1·0

[a] Uncertainties are average deviations of at least four runs.

[b] Uncertainties are maximum errors assessed from the uncertainties in k_T, k_p and C/O. See experimental.

TABLE 2. ACTIVATION QUANTITIES FOR C- AND O-ALKYLATION IN THE REACTIONS OF SODIO-2-CARBETHOXYCYCLANONES WITH ISOPROPYL IODIDE IN DMSO AT 30°[a]

	I-5	I-6	I-8
$\Delta H_c^{\ddagger}$ (kcal/mole)	14·5 ± 0·6	12·8 ± 0·6	17·6 ± 0·8
$\Delta S_c^{\ddagger}$ (e.u.)	−24·2 ± 2·0	−31·2 ± 2·0	−12·2 ± 2·6
$\Delta H_o^{\ddagger}$ (kcal/mole)	15·6 ± 0·6	13·8 ± 0·6	22·0 ± 0·8
$\Delta S_o^{\ddagger}$ (e.u.)	−22·1 ± 2·0	−28·5 ± 2·0	−2·1 ± 2·6

[a] Uncertainties are statistical errors[16] assessed from the average deviations in the individual rate constants over the temp range studied.

DISCUSSION

From the C/O ratio data in Table 1 it may be seen that the ability of the O-alkylation process to compete with the C-alkylation mode in these systems decreases

---

[16] E. L. Purlee, R. W. Taft Jr. and C. A. Defazio, *J. Amer. Chem. Soc.* 77, 837 (1955).

abruptly after the ring size has passed six members (cf. also the C/O ratios for the 7- and 10-membered ring systems, footnote 5). The free energies of activation for the two alkylation processes are most evenly balanced in the 6-membered cycle, $\Delta\Delta F^{\ddagger}$ at 30° for that system being but 0·2 kcal/mole as compared with 0·3 kcal/mole for I-5 and 1·2 kcal/mole for I-8. The response of the C/O ratio to increasing temperature is also of interest; in each case, an increase in temperature favors O-alkylation, a fact which implies that the O-alkylation process has the higher enthalpy of activation but a more favorable, or, at least, comparable, entropy of activation.[17,18] It will also be noted that the *magnitude* of the response of the C/O ratio to the 20° temperature increment varies from 12–14% decrease for I-5 and I-6 to a more pronounced response of 37% for I-8. This result is readily understandable through consideration of the enthalpies of activation for the competing reactions in the three systems (Table 2). Since the C/O ratio is governed by both temperature dependent and temperature independent terms, i.e.,

$$\ln C/O = \ln k_C/k_O = \Delta\Delta H^{\ddagger}_{o-c}/RT + \Delta\Delta S^{\ddagger}_{c-o}/R \tag{11}$$

it follows that the magnitude of the response of the ratio to temperature change will be determined by the change in the temperature dependent term; this change, in turn, will be controlled by the *magnitude* of the difference in the enthalpies of activation, $\Delta\Delta H^{\ddagger}_{o-c}$. For I-8, this difference is 4·2 kcal/mole whereas for I-5 and I-6, the values of $\Delta\Delta H^{\ddagger}_{o-c}$ are but 1·1 and 1·4 kcal/mole.

Examination of the total and individual rate constants summarized in Table 1 reveals some noteworthy points. The values of $k_{T\ corr}$ and of k_C show the same order of reactivity in the anion which we observed earlier in the C-methylation of these compounds in ethanol, i.e. I-8 > I-5 > I-6.[13] The curious inverse relationship between basicity and nucleophilicity for I-5 and I-6 which was commented on at that time persists in the C-isopropylation reactions in DMSO; I-5, the weaker base (by a factor of ca. 20 in EtOH), nonetheless shows a higher nucleophilicity by a factor of almost two. The values of k_P, which might be expected to reflect the basicities of the anions more closely, show a reactivity order I-8 > I-6 $\cong$ I-5, so that even in these reactions the inherently greater basicity of I-6 over that of I-5 appears to be masked by other effects.[19]

The values of k_O show the most striking behavior of all the rate constant values. Two features stand out. First, for a given temperature there is very little difference in the rate constants for O-alkylation as the anion is changed, i.e., at 30°, the values of k_O for I-5,

---

[17] See M. J. S. Dewar, *The Electronic Theory of Organic Chemistry* p. 103. Oxford University Press, London (1949) for an early and lucid discussion of this point. The same analysis of the temperature-dependence of activation free energy differences in terms of activation enthalpies and entropies has been applied to the Sommelet *vs.* Stevens rearrangement pathways available to ylides of quaternary ammonium salts by Zimmerman, *Molecular Rearrangements* (Edited by P. de Mayo) Vol. I; p. 387. Interscience, New York, N.Y. (1963).

[18] We have noted with interest the parallel results in DMSO for the C- and O-alkylation of acetoacetic ester and the *converse* trend for the same alkylations in N-methylpyrrolidone reported recently by Brieger and Pelletier.[8a] The latter result presumably means that in the pyrrolidone solvent the magnitudes of the activation enthalpies are reversed.

[19] Although the acidities of the β-ketoesters conjugate to the bases I-5 and I-6 have not, to our knowledge, been measured in DMSO, it might be expected that the difference would be even more pronounced in the aprotic solvent than in ethanol or water. Cf. Ref. 6, p. 173.

I-6 and I-8 stand in the ratio 1·3:1:0·8 which may be compared with the corresponding ratio of k_c values, 1·7:1:4·4. Secondly, there is no parallelism of k_o with anion basicity; indeed, the most basic enolate, I-8, is the least reactive in O-alkylation at 20° and 30° and just begins to surpass I-6 at 40°. If the magnitude of k_o is to be taken as a measure of the intrinsic nucleophilicity of the oxygen atom of the enolate system, then, clearly, that power has been markedly reduced in the 8-membered ring.

The facts pointed out in the preceding paragraphs also are reflected in the activation parameters for C- and O-alkylation in Table 2 where it can be seen that the competitive nature of the alkylations of I-5 and I-6 may be traced to relatively small $\Delta\Delta H^{\ddagger}_{o-c}$ values and to $\Delta\Delta S^{\ddagger}_{c-o}$ values which slightly favor reaction at oxygen. The corresponding values for I-8 reveal that were it not for a relatively large activation entropy difference (10 e.u.) favoring O-alkylation, this reaction would not show the incursion of the O-alkylation component that it does since the enthalpy of activation is much larger for the reaction at oxygen than for that at carbon.

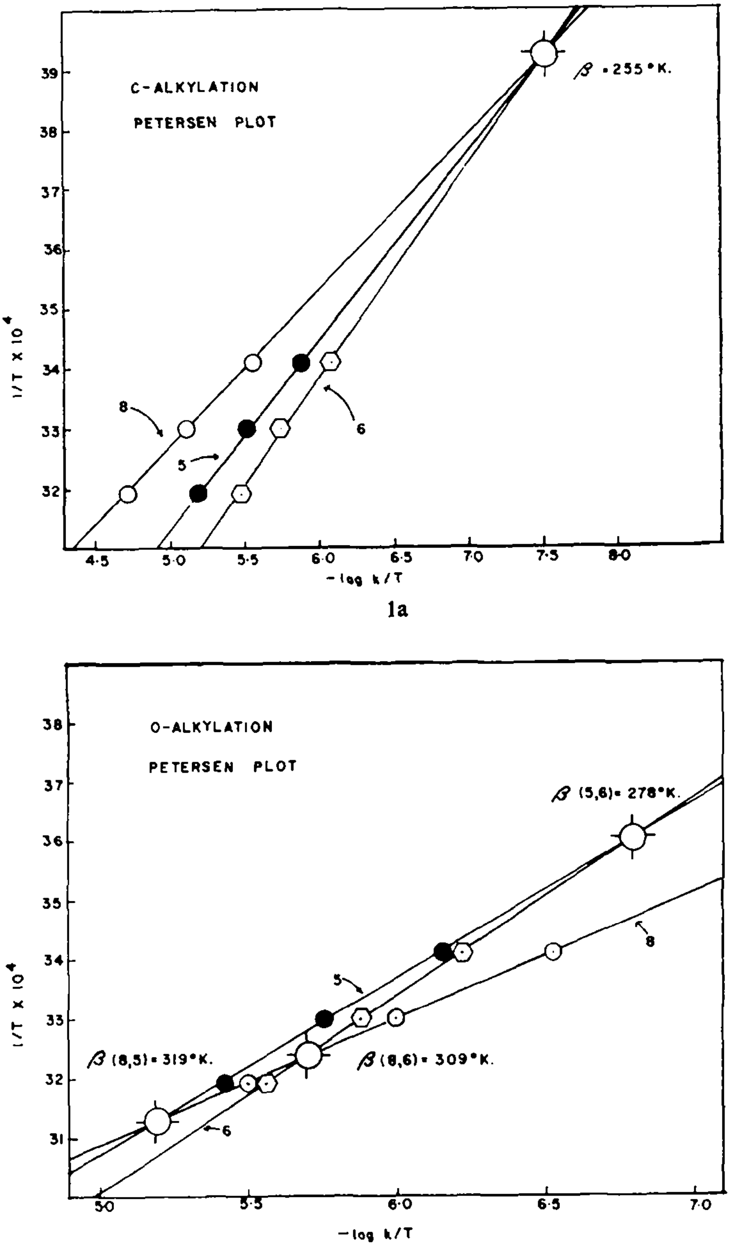
In all three cases, the observed rates of the alkylation reactions are the result of compensating effects in the activation enthalpy and entropy terms and it becomes of interest to examine the exactness of this correlation. In view of the criticism that has been leveled at "isokinetic" relationships in recent times,[20] we have taken special care to assess our errors generously and to apply the criteria suggested for the recognition of spurious correlations arising from random errors.[20] The values of $\Delta H_c^{\ddagger}$ cover a range of 5·1 kcal/mole with a maximum possible error[20a] of 1·3 kcal/mole; for $\Delta H_o^{\ddagger}$, the range of values is 6·9 kcal/mole with the same maximum error. These values satisfy the criterion that the range in values of the activation enthalpies exceed twice the maximum possible error.[20a] When the data are treated by the method of Leffler,[21] the $\Delta H^{\ddagger}$ *vs* $\Delta S^{\ddagger}$ plots for both C-alkylation and O-alkylation give good straight lines with slopes of $\beta = 255$°K for C-alkylation and $\beta = 315$°K for the O-alkylation process. To further test the validity of the correlation we have applied the criterion of Petersen[20b] which requires that a plot of log k/T *vs.* 1/T give a family of straight lines intersecting at the reciprocal of the isokinetic temperature. These plots are shown in Fig. 1. For the reaction of C-alkylation the three lines do intersect at a common point corresponding to a temperature of 255°K (−18°C). The O-alkylation data, while not so well-behaved, still give three points of intersection (two of them quite close-lying), corresponding to three isokinetic temperatures of 319°K (46°C) for the pair I-5, I-8; 309°K (36°C) for the I-6, I-8 pair; and 278°K (5°C) for the I-5, I-6 pair.

The isokinetic temperature of minus 18° for the reaction of C-alkylation lies well below the experimental temperature range (20–40°) and, as anticipated, for reactions studied above the isokinetic temperature, the reaction rates show clear-cut entropy control.[21,22] The isokinetic temperatures for the O-alkylation of the I-5, I-8 and I-6, I-8 pairs, however, are very close to the upper limit of the experimental temperature range. *Therefore, the lack of a marked change in the rate constants for O-alkylation in the series and particularly the anomalous position of* I-8 *in the series noted earlier cannot*

[20a] R. C. Petersen, J. H. Margraf, and S. D. Ross, *J. Amer. Chem. Soc.* **83**, 3819 (1961); [b] R. C. Petersen, *J. Org. Chem.* **29**, 3133 (1964).

[21] J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955). J. E. Leffler and E. Grundwald, *Rates and Equilibria of Organic Reactions* Chap. 9. Wiley, New York, N.Y. (1963).

[22] J. F. Bunnett, *Technique of Organic Chemistry* (Edited by A. Weissberger) Vol. VIII; Part I; p. 207 ff. Interscience, New York, N.Y. (1961).



1a

1b

Fig. 1. Isokinetic plots according to Petersen for the reactions of C-alkylation (top) and O-alkylation (bottom).

be taken as evidence that the O-alkylation process is insensitive to structural change in the anion or that I-8 *is uniquely poor with respect to its oxygen nucleophilicity.* Rather it is likely that these appearances are simply the consequence of an unfortunate coincidence of the experimental temperature and the isokinetic temperature for the O-alkylation process. Support for this explanation is gained from the fact that at the upper limit of the experimental temperature range the values of k_0 for I-6 and I-8 have just begun to show the inversion in magnitude predicted[21,22] when their isokinetic temperature of 36° is crossed while the values of k_0 for I-5 and I-8 are approaching each other closely just below their isokinetic temperature of 46°. Similarly, the increasing difference in the rates for I-5 and I-6 as the reaction temperature is carried further above that isokinetic temperature (5°) can be rationalized. It seems likely that if these reactions could be studied at a much higher or lower temperature, or in another solvent system, quite a different picture of the effect of ring size on reactivity toward O-alkylation would emerge.

While the unwitting choice of an experimental temperature in the isokinetic region for O-alkylation defeated a major purpose of this investigation, the results do serve to reemphasize some of the problems associated with studies of relative reactivities and the importance of extending such studies over a range of temperatures.[22] Special caution in the interpretation of results seems demanded when the changes introduced into the reaction series are steric in nature and relatively small and when their effects are being experienced at more than one reaction site.

EXPERIMENTAL

Reagents. The preparation and properties of the cyclic ketoesters (I-5, I-6, and I-8) have been described earlier.[11] Reagent grade DMSO was further purified by vacuum distillation under N from anhydrous CaO according to the method of Sears *et al.*[8] A middle fraction, b.p. 68°/5 mm, was redistilled under N from NaH for use in the kinetic runs. Isopropyl iodide was purified by repeated distillation from sodium and was stored over Ca metal.[23]

Preparation of the sodium enolates. An all-glass system consisting of a 3-necked flask fitted with a dropping funnel with pressure equalizing side-arm, a fritted glass filter stick, a N inlet and magnetic stirring bar was thoroughly heat-dried and purged with dry N. An amount of Metal Hydrides 50% NaH–oil dispersion equivalent to slightly less than 0·03 moles of hydride was introduced into the flask under a stream of N. The mineral oil was removed by 5 successive additions of anhydrous pet. ether, stirring and filtration through the filter stick under slight N press. To the oil-free hydride overlaid with anhydrous ether, an ethereal solution of 0·03 moles of the β-ketoester was added dropwise and with stirring. After the reaction was complete, the solvent was removed by filtration and the white, solid salt washed thoroughly in the manner described above with anhydrous ether to remove any unreacted ester. After the final wash, the residual Na- enolate was vacuum-dried at room temp *in situ.*

Preparative alkylations. The preparative reactions were carried out in the same manner as the kinetic runs described in detail below except that the reaction mixtures were allowed to stand at room temp for ca. 10 half-lives. Isolation of the alkylation products was accomplished by pouring the reaction mixture (250 ml) into a mixture of 200 ml cold water and 500 ml pet. ether (b.p. 30–60°) and shaking the mixture for 1 hr in a mechanical shaker. The pet. ether layer was separated, washed twice with cold water, dried over molecular sieves (size 4-A) and flash-distilled. Vacuum distillation of the concentrate afforded the alkylation product mixture (contaminated by variable amounts of the original β-ketoester depending on the extent of propene formation and the acidity of the ketoester) in yields of 80% or better. The determination of the number of components in the mixture and the isolation of each component were accomplished by GLC outlined below.

---

[23] *Technique of Organic Chemistry* (Edited by A. Weissberger) 2nd Ed., Vol. VII; p. 249. Interscience, New York, N.Y. (1955).

GLC analysis and isolation. This was carried out with a Perkin–Elmer 154 C Vapor Fractometer. The injection block was heated with an auxiliary 300 watt heater controlled by a variable voltage supply. Helium was the carrier gas in all cases. The columns used for the separation and analysis of the mixtures were 4 m, $\frac{1}{4}$ in diam, Al columns containing 10% Carbowax 1500 on Gas-Chrom-P (Column A) or Perkin–Elmer "C" packing (Column B). The conditions for analysis of the reaction mixtures are given in Table 3 and a typical fractogram is shown in Fig. 2. For isolation purposes, the same packings were used in preparative columns with suitable temp and flow rate modifications.

TABLE 3. GLC ANALYTICAL DATA FOR C- AND O-ISOPROPYL DERIVATIVES OF 2-CARBETHOXYCYCLANONES

Parent Compound	Column	Column Temp	Flowrate ml/min	Block Voltage	Retention Times II n	III n	(min.) IV n
I-5	A	138	120	85	15·0	17·0	7·0
I-6	B	144	75	90	26·8	31·0	20·0
I-8	B	187	60	90	26·0	20·0	17·0

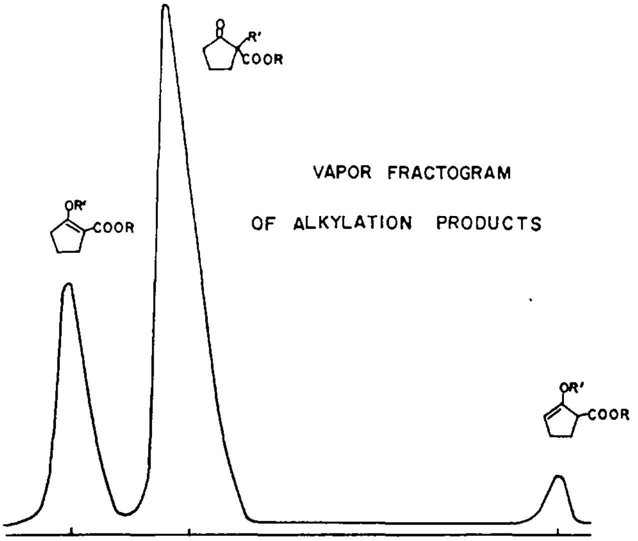


FIG. 2. Vapor fractogram of reaction mixture from the reaction of 2-carbethoxycyclopentanone with isopropyl iodide in DMSO.

Isolation of the 3 alkylation products in each case was accomplished by repetitive trapping and, when necessary, recycling of the fractions. The structures and purities of the isolated products were established by their UV, IR and NMR spectra, summarized in Table 4. That the β,γ-O-derivative (IV n) is not produced by isomerization of the α,β-derivative under GLC conditions was shown by the fact that both pure isomers emerged unchanged upon reinjection into the column.

Kinetic studies

Determination of k_T. To the dried sodium enolate (ca. 0·03 mole) prepared as described above, was added approximately 200 ml purified DMSO and the mixture stirred to effect soln. The soln of Na salt was then transferred to a 250 ml volumetric flask through a fritted disc, vacuum filtration unit attached directly to the original flask. All operations were conducted under a protective N atm. The final soln was made up to 250 ml and equilibrated at the desired temp in a constant temp bath with control of ±0·03°. The enolate concentration of the equilibrated soln was determined by adding a 5 ml aliquot to excess standard 0·1N HCl and back titration to a methyl purple endpoint with standard 0·05N NaOH.

Table 4. Spectral data for C- and O-isopropyl derivatives of 2-carbethoxycyclanones

Compound	UV λ_{max} (ε) mμ	IR[a] $\nu_{C=O\ ket.}$ cm^{-1}	$\nu_{C=O\ ester}$ cm^{-1}	$\nu_{C=C}$ cm^{-1}	NMR[b] $\delta_{-C=C-H}$ ppm (no. H)	$\delta_{-\overset{H}{C}-COOR}$ ppm (no. H)
II-5	299 (56)	1751 s	1723 s	absent	—	—
II-6	275 (30)	1716 vs[c]		absent	—	—
II-8	285 (20)	1709 s	1741 s, 1722 sh	absent	—	—
III-5	255 (12,000)	absent	1705 s, 1688 s	1628 s	absent	absent
III-6	249 (6,300)	absent	1718 s, 1692 sh	1634 m–s	absent	absent
III-8	251 (5,500)	absent	1743 sh, 1723 s, 1707 sh, 1691 s, 1665 sh	1629 m	absent	absent
IV-5	no max, 320–220 mμ	absent	1733 s	1645 m–s	4·43 (1)	3·58 (1)
IV-6	no max, 320–220 mμ	absent	1739 s	1669 m–s	4·68 (1)	2·93 (1)
IV-8	no max, 320–220 mμ	absent	1745 s, 1717 sh	1665 m–s, 1597 sh	4·52 (1)	~3·50 (1)

[a] vs = very strong, s = strong, m = medium, sh = shoulder.

[b] Only the signals relevant to double bond position are given. In all cases, the total areas of the spectra showed integration values for the correct number of hydrogens. The signals of both the vinyl and α-protons in IV-n are complex multiplets.

[c] Unresolved carbonyl envelope of ester and ketone bands. Cf. Ref. 9 for similar results for the methyl derivative.

Stock solns of isopropyl iodide in DMSO were prepared so that 25 ml of a 50 ml stock soln would give the desired initial concentrations of reactants (0·05M enolate and 0·10, 0·15, 0·20, and 0·40M isopropyl iodide) when mixed with 25 ml of the stock enolate soln. The iodide stock soln was prepared with thermally equilibrated DMSO in a 50 ml volumetric flask just prior to a run. A 25 ml aliquot of the standardized Na-enolate soln was transferred to an actinic volumetric flask and treated with an equal volume of the iodide soln. Timing was started when ½ the iodide soln had been added. During the addition, the contents of the flask were swirled rapidly to ensure thorough mixing. Periodically, 5 ml aliquots were withdrawn from the flask, quenched with excess standard acid and the enolate concentrations determined by back titration with standard base. Seven to 10 points were taken in the range of 10–80% reaction. Total rate constants, k_T, were evaluated from plots of log (P)/(E) or, when appropriate, 1/(E), *vs* time from the slopes of the least squares lines. Figure 3 shows a typical plot, that of the 2-carbethoxycyclo-octanone system.

Correction of k_T *for medium dilution effect.* The data in Table 5 illustrate the effect of increasing amounts of isopropyl iodide and the corresponding effect of inert additives on the total rate constant for the reaction of I-6 at 30·4° in DMSO. Table 6 contains the observed total rate constants for I-6 at 20, 30 and 40° and the rate constants corrected for dilution of the medium by isopropyl iodide according to Eq. (8). Corresponding corrections were applied to the observed total rate constants for I-5 and I-8 to obtain the values tabulated in Table 1.

Determination of k_p. The procedure described for the preparation of the reaction mixture was followed in the measurement of the rate of propene formation. However, immediately after mixing of the reagents, 5 ml aliquots (4 to 7 for each run) were sealed in ampules and placed in a constant temp bath. The runs were carried out with equal concentrations of reactants. At intervals, an ampule was removed from the bath and immediately broken in an absorption train of the type described by Hughes *et al.*[18] The propene was swept with a stream of N into cooled receivers containing solns of Br in CCl_4. The final receiver contained an aqueous solution of excess KI to capture any Br vapor swept out of the solns. After the system to which the reaction sample had been

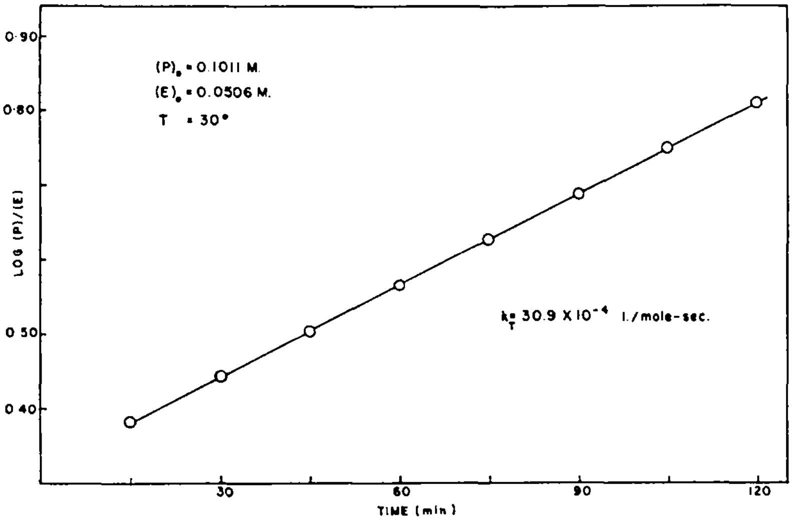


FIG. 3. Second order plot of the reaction of 2-carbethoxycyclooctanone with isopropyl iodide in DMSO at 30°.

TABLE 5. THE EFFECT OF MEDIUM DILUTION ON THE TOTAL RATE CONSTANT FOR THE ALKYLATION OF 2-CARBETHOXYCYCLOHEXANONE WITH ISOPROPYL IODIDE AT 30·4° IN DMSO
$(E)_0 = 0{\cdot}0626$ mole/l

Run	$(P)_0$ mole/l	Additive and mole fraction of additive	$k_T \times 10^4$ l/mole-sec
1	0·1253		12·3
2	0·2506		11·3
3	0·1249	tetrahydrofuran, 0·005	11·8
4	0·1249	benzene, 0·005	11·8
2	0·1253	C_3H_7I,[a] 0·010	11·3

[a] One-half of the original iodide regarded as additive.

added had been swept for 40 min, the solns in the receivers were combined and titrated to a starch endpoint with standard $Na_2S_2O_3$. The difference in Br concentrations between a blank and a sample run was taken as a measure of the propene produced in the reaction in a given time.

The rate constant for propene formation, k_p, was evaluated from these data as illustrated in the following sample calculation for k_p at 30° in the reaction of I-5.

$t = 232 \times 60$ sec $\quad (C_3H_6)_t = 0{\cdot}0037$ mole/l.
$k_{T\,corr} = 17{\cdot}4 \times 10^{-4}$ l/mole-sec.
$(E)_0 = (P)_0 = 0{\cdot}0460$ mole/l.
$(E)_t = (E)_0/[1 + k_{T\,corr}(E)_0 t] = 0{\cdot}0219$ mole/l.
$(E)_0 - (E)_t = 0{\cdot}0241$ mole/l.
$k_p = (C_3H_6)_t\, k_{T\,corr}/[(E)_0 - (E)_t] = 2{\cdot}67 \times 10^{-4}$ l/mole-sec.

The values of k_p, measured at 3 temps for each anion, are summarized in Table 1. Identification of propene as a component of the reaction mixtures was made directly by GLC analysis at 25° in a 4 m column of 1–2% dimethylsulfolane on a Fluoropak-Microbead support.

Alkylation rate constants, k_C *and* k_O. From the experimentally determined rate constants, $k_{T_{corr}}$ and k_p, the sum $k_C + k_O$, was evaluated for each anion at each temp studied. The C/O product

TABLE 6. OBSERVED AND CORRECTED RATE CONSTANTS FOR THE ALKYLATION OF 2-CARBETHOXYCYCLOHEXANONE IN THE PRESENCE OF INCREASING AMOUNTS OF ISOPROPYL IODIDE AT THREE TEMPERATURES

$(E)_0$ mole/l	$(P)_0$ mole/l	$(N_p)_0$	$k_T \times 10^4$ l/mole-sec	$k_{T\,corr} \times 10^4$ l/mole-sec
T = 20·00 ± 0·03°				
0·0536	0·1072	0·008	4·73	5·14
0·0536	0·1072	0·008	4·73	5·14
0·0717	0·1437	0·010	4·58	5·09
0·0717	0·1437	0·010	4·66	5·18
0·0717	0·2843	0·020	4·05	5·06
				Av. 5·12 ± 0·03
T = 30·00 ± 0·03°				
0·0513	0·0513	0·004	11·6	12·0
0·0513	0·0513	0·004	11·8	12·2
0·0691	0·0691	0·005	11·6	12·2
0·0691	0·1381	0·010	10·8	12·0
0·0691	0·1381	0·010	10·8	12·0
0·0673	0·2693	0·019	9·55	11·8
0·0673	0·2693	0·019	9·53	11·8
				Av. 12·0 ± 0·1
T = 40·00 ± 0·03°				
0·0663	0·0663	0·005	27·3	28·8
0·0663	0·0663	0·005	27·7	29·2
0·0638	0·1276	0·009	24·8	27·3
0·0638	0·1276	0·009	24·8	27·3
				Av. 28·3 ± 0·7

ratio was then used to extract the individual rate constants according to Eqs. (6) and (7). The C/O ratio was determined by integration of the vapor fractogram of the reaction mixture from each kinetic run at the end of that run in the following manner. The solution remaining (5–15 ml) was added to a mixture of 100 ml water and 100 ml pet. ether and shaken for 30 min in a mechanical shaker. The pet. ether extract was washed once with 10 ml cold water, dried over molecular sieves, and concentrated in a rotatory evaporator. The concentrate was subjected to GLC analysis under the conditions cited in Table 3. Integration of the peak areas for C- and O-alkylated (III n + IV n) products gave the C/O ratio.[24] Table 7 presents sample data for C/O ratios obtained in this way. The C/O ratios for the three reactions at 3 temps are included in Table 1.

Activation quantities and errors. The Arrhenius activation energy, E_a, for each of the competing reactions was calculated from the slope of the log k *vs* 1/T plot. The enthalpy and entropy of activation were calculated for 30° from the relationships: $\Delta H^\ddagger = E_a - RT$ and $\Delta S^\ddagger = R(\ln k_{rate} - \ln kT/h) + \Delta H^\ddagger/T$. The uncertainties given in Table 1 for $k_{T\,corr}$, k_p and the C/O ratio are average deviations of at least four determinations. In assessing the errors in the individual rate constants, k_c and k_o, the maximum error arising from the combination of errors in $k_{T\,corr}$, k_p and the C/O ratio has been assumed. Although the ratio of k_c/k_o is known with a high precision of ±1%, the relatively large uncertainty in k_p renders the values of the rate constants themselves much less precise. This fact is reflected in the relatively large errors for the activation parameters for each reaction process.

---

[24] The value of the area ratio was shown to be the same as the molar concentration ratio by checks against standard mixtures; agreement was better than 1%. The workup procedure was tested by taking a known amount of a mixture of known C/O ratio through the process. The percent recovery was better than 90% with no change in the C/O ratio.

TABLE 7. SAMPLE DATA OF C/O RATIOS IN THE ALKYLATION OF 2-CARBETHOXYCYCLANONES WITH ISOPROPYL IODIDE AT 30°

I n	$(E)_0$ mole/l	$(P)_0$ mole/l	C/O[a]
I-5	0·0457	0·0457	1·71
	0·0460	0·0460	1·75
	0·0436	0·0873	1·75
	0·0449	0·1798	1·73
			Av. 1·74 ± 0·02
I-6	0·0512	0·0512	1·35
	0·0512	0·0512	1·34
	0·0690	0·1381	1·34
	0·0690	0·1381	1·35
			Av. 1·345 ± 0·005
I-8	0·0500	0·0500	7·72
	0·0501	0·0501	7·75
	0·0505	0·1011	7·64
	0·0505	0·1011	7·73
	0·0505	0·2022	7·66
	0·0505	0·2022	7·79
			Av. 7·72 ± 0·05

[a] For 1-5 and I-6, the areas were measured with a compensating polar planimeter; in the case of I-8, the areas were determined by wt.

Spectral measurements. UV spectra were measured in matched 1 cm silica cells with a Beckman DB spectrophotometer in spectral quality absolute ethanol. Infrared spectra were obtained with a Perkin–Elmer Model 21 instrument on thin film samples. NMR spectra were determined with a Varian A-60 instrument on micro samples in carbon tetrachloride with a TMS internal standard.

Acknowledgements—Support of this investigation under National Science Foundation Grant GP-1517 is gratefully acknowledged. The spectral facilities of the Laramie Petroleum Research Center, U.S. Bureau of Mines, were generously made available for this work; it is a pleasure to express our appreciation to Mr. Francis MacDonald and Mr. Glenn Cook of that institution for their valuable assistance and advice.