

Cyclohexenone Derivatives. Part VI.¹ C-3 and C-1 Alkylation of Hagemann's Ester (Ethyl 2-Methyl-4-oxocyclohex-2-enecarboxylate) with Alkyl Halides and Michael Acceptors

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Reactions of Hagemann's ester with alkyl halides and Michael acceptors under basic conditions have been studied; the ratios of C-1 to C-3 alkylated products have been determined by g.l.c. and n.m.r. spectroscopy. The higher yield of C-1 alkyl esters from Michael reactions in comparison with simple alkylations has been rationalised on the basis of steric and electronic factors in the transition states.

ALTHOUGH alkylation of Hagemann's ester (ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate) has been extensively used in organic synthesis,² no detailed quantitative analysis of the products has previously been

reaction using several base-solvent combinations and both g.l.c. and n.m.r. spectroscopy as analytical tools, and have extended the study to a few Michael reactions for which virtually no data were previously available.† The results are summarised in Tables 1 and 2.

TABLE I

Alkylation of Hagemann's ester with alkyl halides

No.	Alkylating agent	Method ^a	Yield ^b (%)	C-1 Alkylated products (%)	
				G.l.c.	N.m.r.
1	Pr ⁱ I	A	67	30	28
		B	76	28	27 ^c
2	Pr ⁱ Br	B	60	33	28
		A	55	28	25
4	Bu ⁱ I	B	80	24	
		A	65	33	
		C	76	25	23
5	PhCH ₂ Cl	A	90	20	15
		B	90	15	11
		C	80		20 ^c
6	PhCH ₂ ·CH ₂ Br	A	60	0	5 (30 ^c)
		B	87	0	7
		C	63	0	5 ^c
7	ClCH ₂ ·CO ₂ Et	A	80	0	5
		B	85	0	3 ^c
8	BrCH ₂ ·CO ₂ Et	A	74	0	5 ^c
		B	70	0	5
9	Cl[CH ₂] ₃ ·CO ₂ Et	D (30°)	75	0	5
		A	45	0	5
		B	50	0	
10 ^d	Cl[CH ₂] ₂ ·CO ₂ Et	D (60°)	10	0	
		A	60	52	50
		D (60°)	68	51	50
		D (30°)	65	36	40

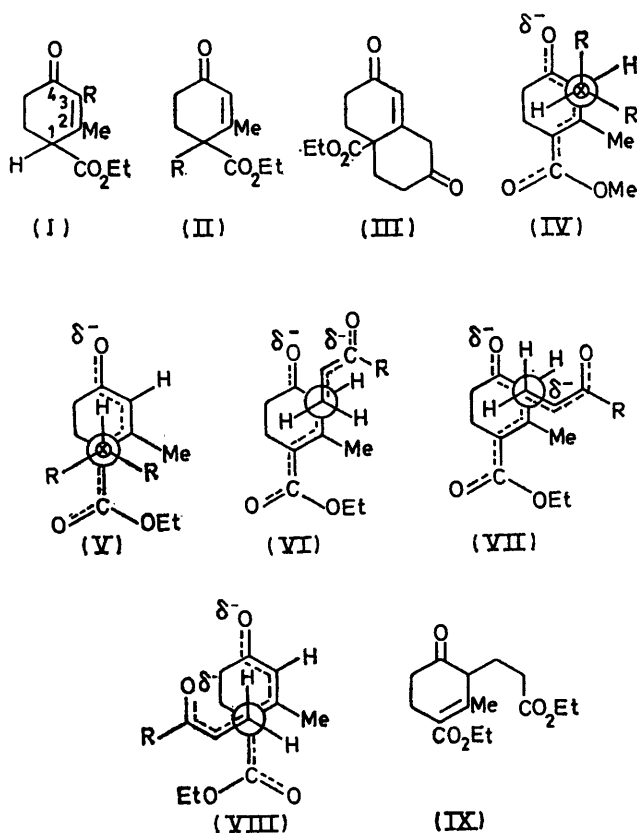
^a Base-solvent systems A, NaOEt-EtOH; B, KOBu^t-Bu^tOH; C, NaH-Me₂N·CHO-C₆H₆; D, NaH-tetrahydrofuran; A—C at reflux temp.; D, temp. shown in parentheses. ^b B.p.s and refractive indices were reported earlier;¹ elemental analyses of the n.m.r. samples are within 1% of theory. ^c Taken from ref. 1. ^d This is apparently a case of Michael addition (see later).

made. We have recently shown^{1,3} by n.m.r. analysis that the alkylation does not proceed exclusively at C-3 as previously assumed;⁴ C-1 alkylation also occurs, in a proportion depending mainly on the nature of the alkylating agents. We have now reinvestigated the

† Traverso *et al.*⁵ condensed ethyl vinyl ketone with Hagemann's ester but did not assign a definite structure to the product.

¹ Part V, G. Sarkar and D. Nasipuri, *J. Indian Chem. Soc.*, 1968, **45**, 200.

² For recent syntheses, see W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Amer. Chem. Soc.*, 1966, **88**, 3859; W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *ibid.*, 1968, **90**, 5872; J. A. Marshall, N. Cohen, and A. R. Hochstetler, *ibid.*, 1966, **88**, 3408; W. S. Johnson, J. M. Cox, D. W. Graham, and H. W. Whitlock, *ibid.*, 1967, **89**, 4524; for other syntheses, see references cited in ref. 3.



Of a given pair of C-3 and C-1 alkylated esters [(I) and (II)] the latter is more resistant to hydrolysis and in many cases separable from the former by partial saponification.³ A few 1-alkyl esters (II; R = Prⁱ, Buⁱ, or CH₂Ph) were thus isolated pure; their structures were confirmed by n.m.r. spectroscopy and the com-

³ D. Nasipuri, G. Sarkar, R. Roy, and M. Guha, *Tetrahedron Letters*, 1966, 927; *J. Indian Chem. Soc.*, 1966, **43**, 343.

⁴ A. Kotz and E. Anger, *Ber.*, 1911, **44**, 466; P. Rabe and E. Pollock, *ibid.*, 1912, **45**, 2924; A. Kotz, K. Blendermann, F. Mahner, and R. Rosenbusch, *Annalen*, 1913, **400**, 72; W. Dieckmann, *Ber.*, 1912, **45**, 2697; J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1957, 1083.

⁵ G. Traverso, G. P. Pollini, and A. Barco, *Farmaco (Pavia), Ed. Sci.*, 1966, **21**, 216 (*Chem. Abs.*, 1966, **64**, 19,439b).

pounds were used as references in g.l.c., where 3-alkyl isomers were always eluted first. Of the other compounds, the keto-diester (I; $R = CH_2 \cdot CH_2 \cdot CO_2Et$) was obtained fairly pure by treatment of a 50 : 50 mixture of the isomers (I and II; $R = CH_2 \cdot CH_2 \cdot CO_2Et$), available from the Michael reaction, with sodium ethoxide. The 1-substituted ester cyclised to the diketone (III)³ and was subsequently removed by alkali. The rest of the products in Table 1 consisted almost exclusively of 3-substituted isomers and needed no further purification for identification by n.m.r. No component of the remaining three mixtures in Table 2 was isolated pure.

elimination of hydrogen chloride followed by Michael addition, and thus falls into the third category, discussed later.

The results of the Michael reactions (Table 2) differ conspicuously from the rest, the yields of C-1 and C-3 adducts being almost equal. Michael addition and the alkylation reaction differ in two important aspects: (i) the Michael adducts may undergo equilibration, whereas alkylation reactions are mostly kinetically controlled; (ii) the transition states of the two reactions are substantially different as regards geometry and charge distribution. No equilibration was in fact

TABLE 2
Products of Michael reactions of Hagemann's ester^a

Michael acceptor	Temp. (°C)	Yield (%)	B.p. (°C) at 2 mmHg	n_D^{20}	Found (%)			Formula	Required (%)			C-1 Alkylation (%)	
					C	H	N		C	H	N	g.l.c.	n.m.r.
$CH_2=CH \cdot CO_2Et$	30	74	175—185	1.4825	63.2	7.7		$C_{15}H_{22}O_5$	63.8	7.8		52	50
$CH_2=CH \cdot COMe$	30	50 ^b	150—155	1.5165	66.6	8.0		$C_{14}H_{20}O_4$	66.7	7.9		43	40
$CH_2=CH \cdot CN$	0	50 ^b	175—180	1.4989	65.7	7.0	6.7	$C_{13}H_{17}NO_3$	66.4	7.2	6.0	49	
	30	50 ^b	175—185	1.4989	65.5	7.5	6.9					50	55
$MeCH=CHCO_2Et$	30	25	165—175	1.4880	64.5	8.0		$C_{16}H_{24}O_5$	64.9	8.1		28	25
	78	40	165—175	1.4885								27	30

^a Sodium ethoxide (0.03—0.05 mol. equiv.) in ethanol was used as base. ^b Appreciable amounts of higher-boiling fractions were obtained in these reactions.

Analysis was carried out on the assumption that the 3-alkyl esters are eluted first in g.l.c., as in the other cases. The results were supported by n.m.r. data. The slight variation between results of g.l.c. and n.m.r. analysis may have been due to the presence of Hagemann's ester in the product as an impurity. Except in the case of reactions with methyl vinyl ketone and acrylonitrile, no appreciable amount of dialkylated product was detected.

The results in the Tables fall into three categories. Reactions with isopropyl and isobutyl halides and benzyl chloride (Table 1, entries 1—5) proceed with substantial amounts (15—30%) of C-1 alkylation; those with phenethyl bromide, ethyl chloro- and bromo-acetate, and γ -chlorobutyrate (entries 6—9) furnish almost exclusively 3-alkyl esters. There is no appreciable solvent effect except perhaps a tendency towards more C-1 alkylation with the sodium ethoxide-ethanol system, and the results agree well with those reported earlier.¹ There is only one big discrepancy (phenethyl bromide alkylation, Table 1, entry 6, method A); in this case we prefer the present values. Alkylations in the second category (Table 1, entries 6—9) are expected to proceed by a pure S_N2 mechanism, whereas those in the first category (entries 1—5) may have some S_N1 character (see, however, ref. 6). The reaction with ethyl β -chloropropionate (entry 10) proceeds essentially by a rapid

observed on heating compound (I; $R = CH_2 \cdot CH_2 \cdot CO_2Et$) with base under Michael conditions. The difference in the results of the two reactions must therefore be traced to the respective transition states. The transition states for alkylation may be depicted by the Newman projections (IV) and (V), viewed along the developing C-C bond, and those for the Michael reaction by projections (VI)—(VIII). In the S_N2 transition states (IV) and (V), the frontal halogen with partial negative charge is denoted X. From electronic considerations, transition states (IV), (VI), and (VII) are decidedly preferable, since the charge density at C-3 is higher than that at C-1. This argument finds support in numerous examples of alkylation⁷ and kinetically controlled protonation⁸ of the enolate anions derived from $\alpha\beta$ -unsaturated ketones,* where the initial attack is generally at the α -carbon atom, of high charge density. With reference to steric effects, a quantitative evaluation of non-bonded interactions is not possible since the hybridisation of the atoms concerned is uncertain in the transition states, as is the geometry. However structure (IV) is qualitatively preferable to (V) as judged from steric interactions in the projection formulae and also from inspection of Dreiding models. Thus for normal alkylation, both electronic and steric effects act so as to stabilise the transition state (IV) and C-3 alkylation

* The analogy is imprecise because of the presence of an ethoxycarbonyl group in Hagemann's ester, but the conclusion may be qualitatively correct.

⁶ N. Kornblum, A. R. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.

⁷ Cf. H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York and Amsterdam, 1965, p. 190, and references cited therein.

⁸ A. J. Birch, *J. Chem. Soc.*, 1950, 1551, 2325; H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 1962, 669; *J. Amer. Chem. Soc.*, 1964, **86**, 1997 and references cited therein; for protonation of similar systems, see C. K. Ingold, E. de Salas, and C. L. Wilson, *J. Chem. Soc.*, 1936, 1328; W. E. Hugh and G. A. R. Kon, *ibid.*, 1930, 775; G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334; J. Hine, *J. Org. Chem.*, 1966, **31**, 1236. Also see ref. 7, p. 66, and C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell, London, 1953, p. 565.

occurs predominantly, giving the unstable $\beta\gamma$ -unsaturated ketone [as (IX)] which subsequently isomerises to the $\alpha\beta$ -unsaturated ketone (I) under the basic conditions. On the other hand, the analogous Michael transition state (VI) for C-3 alkylation, though satisfactory from the foregoing considerations, suffers from a severe polar interaction between the carbonyl oxygen atom and the negative α -carbon atom of the Michael acceptor. Between the two remaining transition states (VII) and (VIII), all other transition states with an alkyl group or side chain over the ring being disregarded on steric grounds, the former (VII), though favoured electronically is destabilised by steric interaction (*syn*-axial type) between the incoming acceptor side chain and the 2-methyl group of Hagemann's ester. As a result, C-1 adducts are formed in comparable yield. The four effective transition states (IV), (V), (VII), and (VIII) have only slight charge dispersal and so are not very sensitive to solvent polarity. Even if they were the effect on isomeric transition states would be the same.

Hagemann's ester was treated with sodium hydride in tetrahydrofuran at 0° and then with ethyl β -chloropropionate, in the hope that the reaction would follow an S_N2 course resulting in C-3 alkylation. A higher percentage of 3-alkyl ester was indeed observed (Table 1, last entry), but not as high as anticipated. Evidently elimination took place faster than substitution. Ethyl crotonate, with a hindered β -carbon atom afforded less C-1 alkylated product than other Michael acceptors presumably because crowding affects the rate of the reaction.

EXPERIMENTAL

Experimental procedures for alkylations by methods A, B, and C (Table 1) were as described in Part V.¹

Alkylation with Sodium Hydride-Tetrahydrofuran (Method D).—To a cold suspension of sodium hydride (1.32 g, 0.055 mol) in tetrahydrofuran (40 ml), Hagemann's ester (13.7 g, 0.075 mol) in the same solvent (10 ml) was slowly added under nitrogen. The orange mixture was stirred for 1 h at room temperature then cooled in an ice-bath, and alkyl halide (0.05 mol) was slowly added. The mixture was stirred for 2 h in the cold and for another 2 h at room temperature or at 60°. The product was decomposed with ice-water, acidified with hydrochloric acid, and extracted with ether. The extract was repeatedly washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated, and the residue was distilled under reduced pressure.

Michael Reactions.—The Michael reactions were carried out in ethanolic solution in presence of 0.03–0.05 mol. equiv. of sodium ethoxide either at 0° or at room temperature for 24 h or at reflux temperature for 2 h (in the case of ethyl crotonate). The product was worked up in the usual way.

Preparation and Attempted Equilibration of Ethyl 3-(2-Ethoxycarbonyl-ethyl)-2-methyl-4-oxocyclohex-2-enecarboxylate (I; R = $\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$).—A 50 : 50 mixture of the esters (I and II; R = $\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$) (14.1 g, 0.05 mol) was mixed with a solution of sodium (1.2 g) in ethanol (40 ml)

and the whole was refluxed for 10 h. Alcohol was removed under reduced pressure and the residue was diluted with cold water and extracted thoroughly with ether. The extract was washed with water, dried, and evaporated, and the residue was distilled to furnish an *oil* (5.0 g), b.p. 175–180° at 2 mmHg (Found: C, 63.9; H, 8.1. $\text{C}_{15}\text{H}_{22}\text{O}_5$ requires C, 63.8; H, 7.8%). This gave a single major peak in g.l.c. and the n.m.r. spectrum showed the complete absence of a vinyl proton peak (τ 4.2). The alkaline mother liquor on acidification afforded a solid which crystallised from benzene-petroleum in white plates, m.p. 172°, identical with the diketone (III).³

The pure ester was refluxed in ethanol with a trace of sodium ethoxide for 24 h under nitrogen and the mixture was then worked up in the usual way. The original ester was recovered unchanged (g.l.c. and n.m.r.).

G.l.c. Analysis.—G.l.c. was carried out on a column (6 ft \times $\frac{1}{4}$ in) of 10% poly(diethylene glycol adipate) on Gas-chrom-Z (60–80 mesh) with nitrogen (40 ml min^{-1} at 20 lb in^{-2}) as carrier gas. An alternative column (6 ft \times $\frac{1}{8}$ in) of Carbowax 20M on Chromosorb was also used. In most cases, the crude products were studied after partial removal of Hagemann's ester. The Michael adducts were all purified by distillation before study. G.l.c. was run at temperatures in the range 150–185°.

N.m.r. Spectroscopy.—N.m.r. spectra were measured with a Varian 60 MHz spectrometer for solutions in [^2H]chloroform with tetramethylsilane as internal standard. Distilled products containing little or no Hagemann's ester (boiling range recorded in the Tables) were used. The same samples were analysed for carbon and hydrogen and checked by i.r. spectra, which showed unsaturated carbonyl bands at 1672–1680 and an ester band at 1730–1740 cm^{-1} . In the case of the methyl vinyl ketone adduct, an additional saturated ketonic band was observed at 1717 cm^{-1} . The substituted Hagemann's ester [mixtures of (I) and (II)] all gave the signals characteristic of the mother ester: vinyl H (q, J 1.5 Hz) at τ 4.05–4.18 and allylic H (t, J 4–5 Hz) at τ 6.7 together accounting for one proton, ester Et at τ 5.8 (2H, q, J 7 Hz) and 8.7 (3H, t, J 7 Hz), allylic Me at τ 7.95 (3H, ill-defined d), and methylenes at τ 7.5–7.8 (4H, m). Other important signals for compounds (I and II; R = Pr¹) were at τ 9.1 (6H, two d, J 7 Hz, CMe_2), for (I and II; R = Bu¹) at τ 9.1 (6H, t, J 7 Hz, CMe_2), for (I and II; R = CH_2Ph) at τ 2.9 (5H, m, aromatic) and 6.35 (2H, s, benzylic), for (I; R = $\text{CH}_2\text{CH}_2\text{Ph}$) at τ 2.9 (5H, m, aromatic) and 7.44 (4H, s, allylic and benzylic methylenes), and for (I; R = $\text{CH}_2\cdot\text{CO}_2\text{Et}$) at τ 6.65br (2H, s, $\text{CH}_2\cdot\text{CO}_2\text{Et}$) and 8.8 (additional ester Me peaks). For compounds (I and II; R = $\text{CH}_2\cdot\text{CH}_2\cdot\text{COMe}$ or $\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$) the $\text{CH}_2\cdot\text{CO}$ and $\text{CH}_2\cdot\text{CN}$ signals showed up as broad singlets at τ 7.45–7.5 and $\text{CO}\cdot\text{CH}_2$ signals at 7.8–7.85, obscured by other methylene peaks. No significant difference was observed in the n.m.r. spectra of a pure component and of the corresponding isomeric mixture except that in the spectrum of the pure compound either the vinyl proton or the allylic proton peak was missing.

We thank Professor E. L. Eliel, Notre Dame University, Indiana, for discussion, Dr. T. W. Doyle, Bristol Laboratories of Canada Limited, for running some of the n.m.r. spectra, and Dr. A. Ghosh, Bose Institute, Calcutta, for helping with g.l.c. measurements.