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Cyclohexenone Derivatives: Part V. Further Studies[1] on Alkylation of Hagemann's Ester

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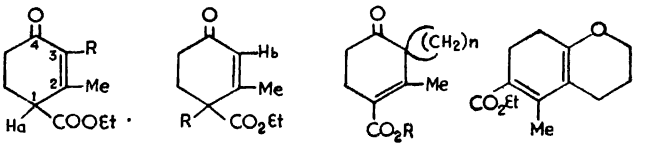
In continuation of previous studies, Hagemann's ester has been alkylated with a variety of alkyl halides. The products, in each case a mixture of C_3- and C_1-substituted esters, are analysed by N.M.R. spectroscopy, the ratio of the two being determined by the relative areas of the vinyl proton at C_3 and allylic proton at C_1. Contrary to previously accepted view, the C_1-alkylation of Hagemann's ester is found to be a general phenomenon and occurs to the extent of 2-51% depending on the nature of alkylating agent and the kind of base used.

Hagemann's ester has also been alkylated with di-, tri-, and tetra-methylene dihalides giving mainly spirocompounds as a result of 3, 3-dialkylation.

Hagemann's ester (I or II, R=H) is known[2] to alkylate exclusively at C_3 in preference to vinylogously active C_1. Evidence concerning appreciable C_1 alkylation was first presented by us[1] during reaction of the ester with ethyl β-halopropionate and isopropyl iodide where the two products (I & II) or derivatives there of were actually separated. In order to see whether this behaviour is general or only restricted to a few alkylating agents, we have now alkylated Hagemann's ester with a variety of alkyl halides using three different base-solvent combinations, namely, sodium ethoxide and ethanol (method A), potassium t-butoxide and t-butanol (method B), and sodium hydride and dimethylformamide (method C). The products (mixtures of I & II) were analysed from N.M.R. spectroscopy by measuring the relative areas of the allylic proton (H_a in I) appearing as a triplet centred at 6.7τ and the vinyl proton (H_b in II) appearing as a singlet at 4.2 τ, which were clearly discernible in most of the spectra. The results of analysis were reproducible and quite reliable as long as R was a heavy group (*vide* Table 1) permitting separation of the alkylated esters from unchanged Hagemann's ester. With smaller alkyl halides like methyl and ethyl iodide, on the other hand, the possibility of the free ester and/or dialkylated products remaining as contaminants could not be fully overruled and the results would be unreliable. Accordingly, these cases have not been included in the present paper, though N.M.R. spectra showed considerable amount of C_1-alkylation in the products (I & II, R=Me, Et, Pr, Bu, Bu^i etc.). These lower boiling esters will be investigated by gas liquid phase chromatography.

The results show that contrary to previously accepted view, C_1-alkylation of Hagemann's ester is quite a general phenomenon and occurs to the extent of 2-51%, depending on the nature of the alkylating agents and the kind of base used. C_1-Alkylation is apparently greater with ethanolic sodium ethoxide (method A) than with the other two base-solvent combinations (alkylation with benzyl chloride by method C however seems to be an exception). One can also see from the table that the reactivity of the alkyl halides

1. Part IV., D. Nasipuri, G. Sarkar, R. Roy, and M. Guha, *This Journal*, 1966, **43**, 383.
2. For references, see Part IV[1]., also R. A. Barnes and M. Sedlak, *J. Org. Chem.*, 1962, **27**, 4562; J.A. Marshall and N. Cohen, *J. Amer. Chem. Soc.*, 1965, **87**, 2773; W. S. Johnson, P. J. Neustaedter and K. K. Schmiegel, *ibid.*, 1965, **87**, 5148.



I II III IV

plays an important role in regulating the product composition. With slower reacting halides such as isopropyl iodide, ethyl β-halopropionate, and phenethyl bromide (entries 1, 4, and 7) and with ethyl acrylate (Michael addition in presence of trace of base, entry 5), C_1-alkylation is appreciably higher than with more reactive halides such as ethyl chloro- and bromo-acetates and benzyl chloride (entries 2, 3, and 6). With the scanty data at our hand, it is not possible to advance any theory to explain this observation. The experiments will nevertheless be a valuable guide for the preparation of substituted Hagemann's esters as regards to the choice of methods.

TABLE I

Entry No	Alkylating Agent	Method	n_D^{30}	Percentage of II	B.p.[sb]
1	Pr^iI	A	1.4820	27.5	130-132°/2mm.
		B	1.4817	27.0	,,
2[a]	$ClCH_2CO_2Et$	A	1.4832	~ 5.0	185-190°/4mm.
		B	1.4832	~ 3.0	,,
3[a]	$BrCH_2CO_2Et$	A	1.4857	~ 5.0	178-180°/2mm.
		B	1.4857	~ 5.0	,,
		C	1.4858	~ 2.0	,,
4	$BrCH_2CH_2CO_2Et$	A	—	30.0[c]	—
5	$CH_2=CHCO_2Et$	A	1.4932	51.0	178-182°/2mm.
6	$PhCH_2Cl$	A	1.5342	11.0	210-215°/5mm.
		B	1.5382	~ 5.0[a]	,,
		C	1.5382	20.0	,,
7	$PhCH_2CH_2Br$	A	1.5312	30.0	180-185°/1mm.
		B	1.5276	10.0	,,
		C	1.5310	~ 5.0[a]	,,

[a]No accurate estimate could be made. [b]B.p. of Hagemann's ester, 120°/2mm. [c] From ref 1.

Recently, Traverso *et al*[3] have condensed ethyl vinyl ketone with Hagemann's ester and obtained a product which was found to differ from 3-substituted ester (I, R=CH_2CH_2 COEt). They represented it as 5-substituted Hagemann's ester apparently without much proof. In the light of the present observation, their product might very well be 1-substituted ester (II, R=CH_2CH_2COEt), which is being investigated.

In another series of experiments, Hagemann's ester was alkylated with a number of polymethylene dihalides in presence of an excess of base, usually potassium t-butoxide. Spirocompounds of the type (III, n=2 & 4) were obtained in high yield when 1,2-dibro-

3. G. Traverso, G. P. Pollini, and A. Barco, *Farmaco* (Pavia), *Ed. Sci.*, 1966, **21**, 216; *Chem. Abstr.*, 1966, **64**, 19439b.

moethane and 1,4-diiodobutane were used. The spiroesters on hydrolysis afforded crystalline acids (as III, R=H), the structures of which were confirmed by their N.M.R. spectra (*vide* experimental section). When trimethylene dibromide was used as alkylating agent, the product was a mixture possibly of the spirocompound (III, n=3) and the dihydropyran derivative (IV). The latter was converted into the corresponding benzodihydropyran carboxylic acid which was a crystalline solid. The structure of the acid was established from its N.M.R. spectrum. This result is in agreement with some recent observation by Newman *et al*[4]. It would be of interest to see whether we can span C_1 and C_3 of Hagemann's ester through a polymethylene chain, by using a sufficiently long α,ω-alkylene dibromide. Experiments on this line are in progress.

EXPERIMENTAL

Hagemann's Ester.—Hagemann's ester was prepared and purified according to the procedure of Smith and Rouault[5].

Alkylation of Hagemagnn's Ester with Alkyl Halides. Method A.—In a typical experiment, sodium (1.15 g., 0.05 mole) was dissolved in absolute ethanol (20 ml.) and the solution cooled to room temperature. Hagemann's ester (9.1 g., 0.05 mole) was dropped into the solution, the mixture stirred for 45 min. and the alkyl halide (0.05 mole) added all at once. The whole was then refluxed on the water-bath for 4-6 hr. Most of the ethanol was removed at the water pump, the residue treated with cold dilute hydrochloric acid, and the organic matter thoroughly extracted with ether. The ethereal layer was dried (Na_2SO_4), the solvent removed on the water-bath, and the residue distilled under reduced pressure. A redistilled sample was used for NMR experiments. The yields and elemental analyses of the different alkyl-Hagemann's esters are given in Table II.

Alkylation with Potassium t-Butoxide. Method B.—To a solution of potassium t-butoxide, prepared from potassium (2.0 g., 0.05 mole) and t-butanol (45 ml.), Hagemann's ester (9.1 g.) was added with shaking, followed by alkyl halides (0.05 mole). The mixture was refluxed on the water-bath for 4-6 hr. preferably under nitrogen. The solvent was partially removed at the water pump and the residue treated with cold dilute sulphuric acid. The organic matter was extracted as usual and distilled in vacuum. The yields and analyses are given in Table II.

Alkylation with Sodium Hydride in Dimethylformamide. Method C. To a suspension of sodium hydride (3.0 g., 50% in oil) in a mixture of benzene (40 ml.) and dimethylformamide (20 ml.), Hagemann's ester (9.1 g.) in benzene (10 ml.) was slowly added under nitrogen. The deep red mixture was cooled, the alkyl halide (0.05 mole) added to it, and the mixture refluxed for 5-6 hr. on the water-bath. The excess of sodium hydride was destroyed by careful addition of acetic acid. The product was then worked up in the same way as in methods A and B. The yields and analyses are given in Table II.

Alkylation with Ethyl Acrylate.—To a well-cooled solution of Hagemann's ester (18.2 g., 0.1 mole) in absolute ethanol (30 ml.) was added dropwise an ethanolic solution of sodium (0.23 g., 0.01 mole). The solution warmed up during the addition and was left overnight at room temperature. Next day, the red reaction mixture was decomposed with

4. M. S. Newman, V. Devries, and R. Darlak, *J. Org. Chem.*, 1966, **31**, 2171.
5. L. I. Smith and G. F. Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 631.

ice and dilute hydrochloric acid and the organic matter extracted with ether. The product was purified by distillation.

TABLE II

Alkylating Agents	Method	Yield %	Analyses			
			Found %		Reqd. %	
			C	H	C	H
Pr^iI	A	67	70.1	9.3	69.6	8.9
	B	76	70.23	9.1		
$ClCH_2CO_2Et$	A	85	61.8	7.8	62.7	7.45
	B	70	63.3	8.2		
$BrCH_2CO_2Et$	A	74	62.1	8.0	62.7	7.45
	B	69	62.1	8.0		
	C	74	62.2	8.0		
$PhCH_2Cl$	A	90	75.0	7.5	75.0	7.4
	B	90	75.2	7.8		
	C	79	75.3	7.6		
$PhCH_2CH_2Br$	A	60	75.2	8.0	75.5	7.7
	B	87	75.0	7.8		
	C	63	75.8	7.3		
$CH_2=CHCO_2Et$	A	80	63.2	8.0	63.5	7.8

Alkylation of Hagemann's Ester with Ethylene Dibromide. Hagemann's ester (18.2 g., 0.1 mole) was added to a solution of potassium t-butoxide prepared from potassium (12.0 g., 0.3 mole) and t-butanol (250 ml.), followed by ethylene dibromide (18.8 g., 0.1 mole). The mixture was refluxed on the water-bath for 4 hr. Most of the solvent was removed at the water pump, the residue decomposed with cold dilute acid and extracted with ether. The ethereal extract was washed with a solution of sodium bisulphite and dried ($Na_2SO)_4$. The following two fractions were collected: a fore-run (5.0 g.), b.p. 120-150°/3 mm. and a middle run (15.0 g., 69%), b.p. 155°/3mm. The latter analysed for the *spiro-ester* (III, n=2, R=Et) (Found: C, 69.2 ; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%).

Preparation of the Spiro-acid (III, n=2, R=H).—The above ester (5.0 g.) and 10% ethanolic potassium hydroxide (30 ml.) were refluxed on the water-bath under nitrogen for 6 hr. The ethanol was removed under suction and the free *acid* (III, n=2, R=H) liberated by the addition of concentrated hydrochloric acid. It was crystallised from dilute acetone in colourless needles, m.p. 147° (Found: C, 66.6; H, 6.4. $C_{10}H_{12}O_3$ requires C, 66.7; H, 6.60%); the N.M.R. spectrum showed a singlet (1 H) at -1.86 τ (COOH), multiplet (4 H) at 7.25τ ($-COCH_2CH_2C=$), a sharp singlet (3H) at 8.02 τ ($=C-CH_3$), two triplets (2 H+2 H), one centred at 8.38τ and the other at 8.56 τ (cyclopropane ring protons).

Alkylation of Hagemann's Ester with 1,4-Diiodobutane. The condensation was carried out in the same way as above. From diiodobutane (31.0 g., 0.133 mole), Hagemann's ester (18.2 g., 0.1 mole), and potassium t-butoxide from potassium (12.0 g., 0.3 mole) and t-butanol (250 ml.), the following fractions were obtained: a fore-run (6.0 g.), b.p. 130-150°/3 mm. and a middle run (III, n=4, R=Et) (15.0 g., 63%); (Found: C, 71.0; H, 8.7. $C_{14}H_{20}O_3$ requires C, 71.2 ; H, 8.5%). The *ester* (5.0 g.) was hydrolysed as before with 10%

ethanolic potassium hydroxide to afford the *spiro- acid* (III, n=4, R=H) which crystallised from dilute methanol in small needles, (2.7 g.), m p. 127° (Found: C, 71.3; H, 8.8. $C_{11}H_{20}O_3$ requires C, 71.2 ; H, 8.7%); the N. M.R. spectrum showed the following peaks: a singlet (1 H) at -2.6τ (COOH), multiplet (4 H) at 7.21τ ($COCH_2CH_2C=$), a sharp singlet (3 H) at 8.0τ (=C-CH_3), and multiplets (8 H) at 7.75 and 8.05τ (cyclopentane methylenes).

Alkylation of Hagemann's Ester with Trimethylene Dibromide.—By condensation of trimethylene dibromide (26.8 g., 0.133 mole) with Hagemann's ester (18.2 g.) in presence of potassium t-butoxide (0.3 mole) as above, the following fractions were obtained : (i) a fore-run (5.0 g.), b.p. 120-140°/3mm. and (ii) a viscous oil (18.0 g.), b p. 165°/3mm.; the latter analysed for either the *spiro-compound* (III, n=3, R=Et) or the *dihydropyran* derivative (IV) (Found: C, 70.0; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70 3, H, 8.1%). Thin layer chromatography in different solvents gave two well-separated spots. No attempt was made to separate the two components. The mixture (1.0 g.) was mixed with sulphur (0·176 g) and heated in a metal bath at 200-250° for 1 hr. The dark red product was distilled and hydrolysed with ethanolic potassium hydroxide to afford a semisolid mass (0.6 g.). This was crystallised from benzene-petroleum and the *benzodihydropyran carboxylic* acid was obtained as white powder, m.p. 207° (Found: C 68.9; H, 6.2. $C_{11}H_{12}O_3$ requires C, 68.8.; H, 6.25%). The N. M. R. spectrum consisted of the following peaks: a singlet (1 H) at -2.0τ (COOH), a doublet (1 H) centred at 2.1 τ and another doublet (1 H) at 3.28 τ (J=8.5 cps) (two adjacent aromatic protons), a triplet (2 H) at 5.8 τ (-OCH_2-), another triplet (2 H) at 7.28τ ($ArCH_2$-), a sharp singlet (3 H) at 7.45 τ (Ar-CH_3) and a multiplet (2 H) at 7.94τ(remaining methylene protons).

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