

EFFECT OF AMIDES ON THE BROMINATION OF METHYL  
ALKYL KETONES

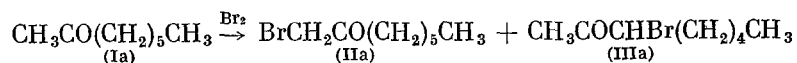
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UDC 541.12.038:542.944:546.14:547.284

Previously [1, 2] it was shown that a mixture of isomeric bromides, with a predominance of the bromomethyl ketones, is formed when methyl ketones are treated with Br<sub>2</sub> in MeOH solution.

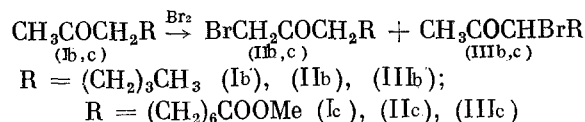
In order to increase the relative yield of the bromomethyl ketones we studied in the present paper the effect of amides, capable of giving complexes with Br<sub>2</sub> [3-5], on the structural direction of the bromination of methyl hexyl ketone (Ia) in MeOH medium. The reaction was run in the presence of equimolar amounts of carboxamides, urea or HMPA at 20°C until all of the Br<sub>2</sub> had disappeared, and then the reaction mixture was treated with water for 20 h to hydrolyze the ketal impurities [1, 2]. The mixture of isomeric bromination products, namely 1-bromo-2-octanone (IIa) and 3-bromo-2-octanone (IIIa), was isolated by extraction with CH<sub>2</sub>Cl<sub>2</sub> and then subjected to GLC analysis (Table 1). From the data in Table 1 it follows that all of the studied amides, except HMPA, retard the bromination of (Ia) and substantially increase the amount of (IIa). In contrast, HMPA (expt. 3) accelerates the bromination of (Ia) and noticeably decreases the relative yield of (IIa). In their effect on the bromination of the CH<sub>3</sub> group in (Ia) the N-unsubstituted amides (expts. 7, 8, 11) surpass the N-substituted amides (expts. 4, 5, 10). Urea has an especially great effect, which permits obtaining a (IIa) that is contaminated with (IIIa) to the extent of only ~20% (expt. 11).

Besides the structural characteristics of the amides, the amount of employed amide and the presence of moisture in the MeOH also affect the (IIa)/(IIIa) ratio.



In the case of urea the highest relative yield of (IIa) is reached when the bromination is run in 99% MeOH and 2 moles of the amide is used. The (IIa)/(IIIa) ratios as a function of the number of moles of urea are: 72:38 (0.5 mole), 82:18 (1 mole), 85:15 (2 moles), 79:21 (3 moles).

Urea also facilitates the bromination of the methyl group of methyl amyl ketone (Ib) and the methyl ester of 9-ketodecanoic acid (Ic).



The reaction of (Ib, c) with Br<sub>2</sub> in 99% MeOH in the presence of an equimolar amount of urea at 20°C gives a mixture of isomeric bromoketones (IIb, c) and (IIIb, c) in a ratio of 82:15 and 72:28. Under the same conditions, but in the absence of urea, the ratios of (IIb, c) and (IIIb, c) are 43:57 and 50:50.

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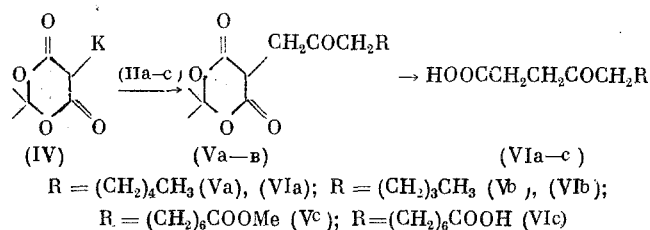
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya*, No. 2, pp. 454-456, February, 1984. Original article submitted March 3, 1983.

TABLE 1. Bromination of (Ia) in the Presence of Amides in MeOH\*

Expt. no.	Amide	Bromination time	(IIa)/(IIIa) ratio
1	—	30s †	43:57
2	—	3min †	47:53
3	HMPA	3s †	25:75
4	Diethylacetamide	4h	60:40
5	DMF	10 min	66:34
6	$\alpha$ -Pyrrolidone	1 h	69:31
7	Acetamide	1,5 h	70:30
8	Formamide	24 h	71:29
9	»	24 h	70:30
10	Methylurea	2 h	80:20
11	Urea	2 h	82:18
12	»	2 h	81:19

\*Experiments 2, 9, and 12 were run in abs. MeOH, and the others were run in 99% MeOH.

†Strongly exothermic reaction.



Treatment of a mixture of bromoketones (IIa-c) and (IIIa-c) in aqueous DMF with the K salt of Meldrum's acid (IV) and subsequent hydrolytic cleavage of the alkylation products (Va-c) as described in [6] gave the corresponding  $\gamma$ -keto acids (VIa-c).

#### EXPERIMENTAL

The PMR spectra were taken on Varian DA-60-IL and Tesla BS-467 instruments. The GLC analyses were run on an LKM-8MD chromatograph equipped with a flame-ionization detector; the 1 m  $\times$  3 mm stainless steel column was packed with 5% Silicone SE-30 deposited on Chromaton N-AW, 0.160-0.300 mm (123-124 $^\circ$ ); N<sub>2</sub> was the carrier gas.

Mixture of 1-Bromo-2-octanone (IIa) and 3-Bromo-2-octanone (IIIa). With stirring, 0.95 g of urea and 0.8 ml of Br<sub>2</sub> were added in succession to a solution of 2 g of methyl hexyl ketone (Ia) in 4.5 ml of 99% MeOH, the mixture was stirred at  $\sim$ 20 $^\circ$ C until the Br<sub>2</sub> disappeared ( $\sim$ 2 h), 1 ml of water and 4.5 ml of MeOH were added, and the mixture was allowed to stand for 20 h at 20 $^\circ$ C. The solution was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with aqueous NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub>, and evaporated in vacuo. We obtained 2.6 g of an oily mixture of (IIa) and (IIIa). PMR spectrum (CCl<sub>4</sub>,  $\delta$ , ppm): 3.76 s (BrCH<sub>2</sub>CO), 4.15 t (COCHBr) [6]. Based on the integral intensities of these signals the (IIa)/(IIIa) was 79:21, and 82:18 when based on the GLC data.

Mixture of 1-Bromo-2-heptanone (IIb) and 3-Bromo-2-heptanone (IIIb). With stirring, 1.05 g of urea and 0.85 ml of Br<sub>2</sub> were added in succession to a solution of 2 g of methyl amyl ketone (Ib) in 4.5 ml of 99% MeOH, the mixture was stirred until the Br<sub>2</sub> disappeared (1.5 h), and after the above-described treatment we obtained 2.5 g of an oily mixture of (IIb) and (IIIb). PMR spectrum (CCl<sub>4</sub>,  $\delta$ , ppm): 3.84 s (BrCH<sub>2</sub>CO), 4.18 t (COCHBr). Based on the integral intensities of these signals and the GLC data the (IIb)/(IIIb) ratio was 82:18.

Mixture of Methyl Esters of 8-Bromo- and 10-Bromo-9-ketodecanoic Acids (IIIc) and (IIc). With stirring, 0.6 g of urea and 1.5 g of Br<sub>2</sub> were added in succession to a solution of 1.9 g of methyl 9-keto-decanoate [7] in 9 ml of 99% MeOH, the mixture was stirred until the Br<sub>2</sub> disappeared (8 h), and after the above indicated treatment we obtained 2.2 g of an oily mixture of (IIc) and (IIIc) [6]. PMR spectrum (CCl<sub>4</sub>,  $\delta$ , ppm): 3.76 s (BrCH<sub>2</sub>CO), 4.08 m (COCHBr). Based on the integral intensities of these signals the (IIIc)/(IIc) ratio was 28:72.

4-Ketodecanoic Acid (VIa) was obtained by a modification of the method given in [6]. With stirring, 0.4 g of Et<sub>4</sub>Ni, 3.6 g of Meldrum's acid, 16 ml of DMF, and 2.4 g of the above described mixture of bromoketones (IIa) and (IIIa) were added in succession to a solution of 1.1 g of KOH in 4 ml of water, the mixture was allowed to stand for 72 h at ~20°C, diluted with water, treated with excess K<sub>2</sub>CO<sub>3</sub>, and extracted with benzene. The alkaline layer was acidified with conc. HCl and extraction with benzene gave 2.2 g of crude alkylation product (Va). The latter was mixed with 3 ml of water and 10 ml of AcOH, refluxed for 4 h, cooled to ~20°C, diluted with water, extracted with benzene, and the extract was evaporated in vacuo. The residue was treated with water, and the precipitate was filtered and dried in the air to give 0.7 g of (VIa), mp 67-68°C (from ether at -50°C) (cf. [6]). PMR spectrum (CD<sub>3</sub>OD), δ, ppm): 0.82 t (CH<sub>3</sub>), 1.02-1.70 m (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.22-2.78 m (CH<sub>2</sub>CO, CH<sub>2</sub>COOH).

4-Ketononanoic Acid (VIb). With stirring, 0.4 g of Et<sub>4</sub>Ni, 3.6 g of Meldrum's acid, 16 ml of DMF, and 2.5 g of a mixture of (IIb) and (IIIb) were added in succession to a solution of 1.1 g of KOH in 4 ml of water, the mixture was allowed to stand for 30 h at ~20°C, and after the above-described treatment we obtained 0.8 g of (VIb), mp 67-68°C (from ether at -70°C) (cf. [8]). PMR spectrum (CD<sub>2</sub>OD, δ, ppm): 0.83 t (CH<sub>3</sub>), 1.30 m (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.52 m (CH<sub>2</sub>COOH, CH<sub>2</sub>CO).

4-Ketododecanedioic Acid (VIc). With stirring, 3.6 g of Meldrum's acid, 16 ml of DMF, 0.4 g of Et<sub>4</sub>Ni, and 2 g of a mixture of (IIc) and (IIIc) were added in succession to a solution of 1.1 g of KOH in 4 ml of water, and the mixture was allowed to stand for 24 h at 20°C, diluted with water, treated with excess K<sub>2</sub>CO<sub>3</sub>, and extracted with benzene. The alkaline layer was acidified with conc. HCl and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and then evaporated in vacuo to give the crude alkylation product (Vc). The latter was mixed with 20 ml of AcOH and 5 ml of water, refluxed for 3 h, 3 ml of conc. HCl was added, the mixture was refluxed for another 3 h, cooled to ~20°C, extracted with ethyl acetate, and the extract was dried over MgSO<sub>4</sub> and evaporated. We obtained 0.8 g of (VIc), mp 106-109°C (from ether at -70°C) (cf. [6]). PMR spectrum (CD<sub>3</sub>OD, δ, ppm): 1.20 m [(CH<sub>2</sub>)<sub>5</sub>], 1.98-2.80 m (2CH<sub>2</sub>CO, 2CH<sub>2</sub>COOH).

#### CONCLUSIONS

The bromination of methyl alkyl ketones in methanol medium in the presence of urea, methylurea or carboxamides gives a mixture of the 1-bromo- and 3-bromo-2-alkanones in a 70-80:30-20 ratio.

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