

Reactions of 5,5-dimethyl-1,3-cyclohexanedione anion with substituted benzyl bromides

P. HRNČIAR and K. FABIANOVÁ

*Department of Organic Chemistry, Faculty of Natural Sciences,
Komenský University, 801 00 Bratislava*

Received 29 October 1975

Reactions of 5,5-dimethyl-1,3-cyclohexanedione anion with substituted X-benzyl bromides in acetone were carried out. Under the applied experimental conditions all four possible benzyl derivatives were formed except for the reactions with *p*-methoxybenzyl bromide. It was found that the substituent X affected the C/O ratio of the formed derivatives according to the Kornblum rule and $\log C/O = f(\sigma^+)$. In the reactions with *m*-substituted X-benzyl bromides to the second degree, a partial steric hindrance was observed on the softer carbon nucleophilic centre.

Были осуществлены реакции аниона 5,5-диметил-1,3-циклогександиона с замещенными X-бензилбромидами в ацетоне. В условиях, указанных в экспериментальной части, образуются все четыре из возможных бензилпроизводных за исключением реакций с *p*-метоксибензилбромидом. Было обнаружено, что заместитель X влияет на отношение C/O в образующихся производных в согласии с правилом Корнблума и что $\log C/O = f(\sigma^+)$. При протекании реакции до второй степени с *m*-замещенными X-бензилбромидами частично проявляются стерические препятствия на более мягком нуклеофильном центре углерода.

It is known that in a reaction of an ambident anion with an electrophile the ratio of compounds formed on the softer and the harder nucleophilic centres depends considerably on the nature of the electrophile besides other various effects. Generally, the harder the electrophilic centre, the greater portion reacts with the hard nucleophilic centre and *vice versa* [1]. According to Kornblum [2], at mutual interaction of an ambident anion with an electrophilic agent the increase of S_N1 nature of the transition state increases the tendency to react with the more electronegative atom. Inversely, the increase of S_N2 nature of the transition state increases the tendency to react with the less electronegative atom.

The validity of this rule was confirmed on several examples. It is to be noted that attention was paid mainly to those reactions where the softness or hardness of the electrophilic centre varied with the nature of the nucleophile [3—7]. For example, it was found [6, 7] that on alkylation of the anion of ethyl acetoacetate in various polar solvents the proportion of O-alkylation increased with varying X at the same R and the same experimental conditions in the series



Less attention was paid to the problem how the nature and mainly the electron effects of R affected the ratio of products formed in the reaction with the softer and the harder nucleophilic centre of an ambident anion. Recently, some works appeared which did not approve of the Kornblum rule concerning the effect of R on the ratio of products formed in the reaction on the harder and the softer nucleophilic centres. *Cardillo* [8] and *Le Noble* [3] pointed to the fact that allyl and benzyl halides, which inclined to S_N1 mechanism more than alkyl halides, reacted more rapidly on the softer centre than alkyl halides. It is to be noted, however, that benzyl and allyl halides are ready to react also in reactions with S_N2 mechanism.

The electron effects, induced by changes on the electrophilic centre R, on the ratio C/O in the reaction of the anion of a β -dicarbonyl compound with an electrophile R—X were not studied thus far. Therefore, we carried out the reactions of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) anion with substituted X-benzyl bromides in order to find out the effect of softness and hardness of the electrophilic centre on the ratio C/O of the products formed.

Experimental

Infrared spectra were measured on a UR-20 spectrophotometer (Zeiss, Jena) in chloroform.

The $^1\text{H-NMR}$ spectra were taken on a Tesla BS-487A spectrophotometer at 80 MHz. The proportion of compounds *II* and *III* was determined on the basis of their $^1\text{H-NMR}$ spectra according to the formula

$$\% X = \frac{I_{X(N_Y M_X)} \cdot 100}{I_{Y(N_X M_Y)} + I_{X(N_Y M_X)}$$

where $I_{(X, Y)}$ = height of the integral record of the considered group in mm,

$M_{(X, Y)}$ = molecular mass,

$N_{(X, Y)}$ = number of protons in the considered group.

Reactions of dimedone anion with X-benzyl bromides

Into a three-necked flask, dimedone (5 mmoles), acetone (50 ml), anhydrous potassium carbonate (15 mmoles) and, within 10 min, X-benzyl bromide (X = H, *p*-NO₂, *m*-Cl, *p*-Cl, *p*-Br, *p*-CH₃, *m*-CH₃, *p*-OCH₃) (10 mmoles) were added. The reaction mixture was then heated at $40 \pm 1^\circ\text{C}$ for 3 hrs under stirring. Then it was filtered and the solvent was distilled off. The dry residue was dissolved in benzene (3 × 30 ml); some portion of it was insoluble.

The benzene solution was evaporated to 30 ml and analyzed chromatographically on a column of aluminium oxide (Brockmann, Reanal Budapest). Benzene or, in the case when X = *p*-NO₂, Cl, Br, benzene—chloroform (1:1) were used as eluents. The compound *IV* (2,2-di-(X-benzyl)-5,5-dimethyl-1,3-cyclohexanedione) was eluted first and then a mixture of compounds *III* and *II* (2-(X-benzyl)-3-(X-benzyloxy)-5,5-dimethyl-2-cyclohexen-1-one and 2-(X-benzyloxy)-5,5-dimethyl-2-cyclohexen-1-one). The proportion of the derivatives *II* and *III* in the mixture was determined from the $^1\text{H-NMR}$ spectra or by a further chromatographic separation on aluminium oxide using benzene—petroleum ether (20:1) as eluent.

Table 1

Analytical data of compounds I—IV

Compound	X	Formula	M	Calculated/found		M.p., °C Kofler	$\nu(\text{C}=\text{O})$ cm^{-1}	$\nu(\text{C}=\text{C})$ cm^{-1}
				% C	% H			
<i>Ia</i>	<i>p</i> -NO ₂	C ₁₅ H ₁₇ NO ₂	275.25	65.44	6.65	183—185	1714 ^a	
				65.32	6.24		1745	
<i>Ib</i>	<i>p</i> -Cl	C ₁₅ H ₁₇ ClO ₂	264.73	68.05	6.47	188—189	1710 ^a	
				68.20	6.53		1744	
<i>Ic</i>	<i>p</i> -Br	C ₁₅ H ₁₇ BrO ₂	310.15	58.27	5.54	204—205	1710 ^a	
				58.68	5.44		1745	
<i>Id</i>	<i>m</i> -Cl	C ₁₅ H ₁₇ ClO ₂	264.73	68.05	6.47	175—176	1712 ^a	
				68.17	6.54		1742	
<i>Ie</i>	H	C ₁₅ H ₁₈ O ₂	230.25	78.34	6.91	162—163	1712 ^a	
				78.26	6.98		1744	
<i>If</i>	<i>p</i> -CH ₃	C ₁₆ H ₂₀ O ₂	242.25	78.65	8.24	225—226	1708 ^a	
				78.92	8.09		1738	
<i>Ig</i>	<i>m</i> -CH ₃	C ₁₆ H ₂₀ O ₂	242.25	78.65	8.24	154—155	1710 ^a	
				78.68	8.31		1740	
<i>Ih</i>	<i>m</i> -OCH ₃	C ₁₆ H ₂₀ O ₃	258.25	73.81	7.74	155—156	1708 ^a	
				73.62	7.53		1738	
<i>IIa</i>	<i>p</i> -NO ₂	C ₁₅ H ₁₇ NO ₂	275.25	65.44	6.65	72—74	1652	1621
				65.32	6.24			
<i>IIb</i>	<i>p</i> -Cl	C ₁₅ H ₁₇ ClO ₂	264.73	68.05	6.47	68—69	1649	1620
				68.18	6.41			
<i>IIc</i>	<i>p</i> -Br	C ₁₅ H ₁₇ BrO ₂	310.15	58.27	5.54	91—92	1650	1620
				58.62	6.63			
<i>II_o</i> <i>II_d</i>	<i>m</i> -Cl	C ₁₅ H ₁₇ ClO ₂	264.73	68.05	6.47	32—33	1648	1621
				68.12	6.32			
<i>Ile</i>	H	C ₁₅ H ₁₈ O ₂	230.25	78.34	6.91	41—42	1645	1625
				78.12	6.82			

Table 1 (Continued)

Compound	X	Formula	M	Calculated/found		M.p., °C Kofler	$\nu(\text{C}=\text{O})$ cm ⁻¹	$\nu(\text{C}=\text{C})$ cm ⁻¹
				% C	% H			
<i>IIf</i>	<i>p</i> -CH ₃	C ₁₆ H ₂₀ O ₃	242.25	78.65 78.47	8.24 8.14	29—31	1643	1620
<i>Ilg</i>	<i>m</i> -CH ₃	C ₁₆ H ₂₀ O ₂	242.25	78.65 78.54	8.24 8.40	Oil	1650	1625
<i>IIh</i>	<i>m</i> -OCH ₃	C ₁₆ H ₂₀ O ₃	258.25	73.81 73.89	7.74 7.49	Oil	1649	1622
<i>IIi</i>	<i>p</i> -OCH ₃	C ₁₆ H ₂₀ O ₃	258.25	73.81 74.02	7.74 7.91	23—25	1648	1622
<i>IIIa</i>	<i>p</i> -NO ₂	C ₂₂ H ₂₂ N ₂ O ₆	378.34	64.39 64.54	5.44 5.32	120—122	1652	1635
<i>IIIb</i>	<i>p</i> -Cl	C ₂₂ H ₂₂ Cl ₂ O ₂	389.32	67.61 67.69	5.69 5.42	77—78	1648	1622
<i>IIIc</i>	<i>p</i> -Br	C ₂₂ H ₂₂ Br ₂ O ₂	478.21	55.23 55.47	4.63 4.70	70—71	1650	1620
<i>IIId</i>	<i>m</i> -Cl	C ₂₂ H ₂₂ Cl ₂ O ₂	389.32	67.61 67.42	5.69 5.45	85—86	1649	1621
<i>IIIe</i>	H	C ₂₂ H ₂₄ O ₂	320.34	82.46 81.96	7.23 7.69	102—103	1650	1625
<i>IIIf</i>	<i>p</i> -CH ₃	C ₂₄ H ₂₈ O ₂	348.35	82.71 82.75	8.09 8.07	93—94	1648	1622
<i>IIIg</i>	<i>m</i> -CH ₃	C ₂₄ H ₂₈ O ₂		82.71 82.89	8.09 8.15	65—66	1640	1620
<i>IIIh</i>	<i>m</i> -OCH ₃	C ₂₄ H ₂₈ O ₄	386.35	75.76 75.74	7.44 7.61	93—94	1646	1622
<i>IIIi</i>	<i>p</i> -OCH ₃	C ₂₄ H ₂₈ O ₄	380.35	75.76 75.69	7.44 7.39	120—121	1647	1620
<i>IVa</i>	<i>p</i> -NO ₂	C ₂₂ H ₂₂ N ₂ O ₆	378.34	64.39 64.21	5.44 5.20	182—184	1706.5 1732.0	

Table 1 (Continued)

Compound	X	Formula	M	Calculated		M.p., °C cm ⁻¹	ν(C=O) cm ⁻¹	ν(C=C) cm ⁻¹
				% C	% H			
IVb	<i>p</i> -Cl	C ₂₂ H ₂₂ Cl ₂ O ₂	389.32	67.61	5.69	144—146	1705.0	
				67.70	5.61		1735.0	
IVc	<i>p</i> -Br	C ₂₂ H ₂₂ BrO ₂	478.21	55.23	4.63	160—161	1705.0	
				55.75	4.59		1734.0	
IVd	<i>m</i> -Cl	C ₂₂ H ₂₂ Cl ₂ O ₂	389.32	67.61	5.69	135—136	1705.0	
				67.21	5.68		1735.5	
IVe	H	C ₂₂ H ₂₄ O ₂	320.34	82.46	7.23	135—136	1700.0	
				81.96	7.55		1730.0	
IVf	<i>p</i> -CH ₃	C ₂₄ H ₂₈ O ₂	348.35	82.71	8.09	164—166	1700	
				82.69	8.15		1728	
IVg	<i>m</i> -CH ₃	C ₂₄ H ₂₈ O ₂	348.35	82.71	8.09	95—97	1701	
				82.89	8.12		1731	
IVh	<i>m</i> -OCH ₃	C ₂₄ H ₂₈ O ₄	380.35	75.76	7.44	127—128	1699.0	
				75.68	7.80		1729.0	
IVi	<i>p</i> -OCH ₃	C ₂₄ H ₂₈ O ₄	380.35	75.76	7.44	155—156	1701.5	
				75.82	7.55		1729.0	

a) For diketo form.

Table 2

Results of the reaction of 5,5-dimethyl-1,3-cyclohexanedione anion with X-benzyl bromide in acetone

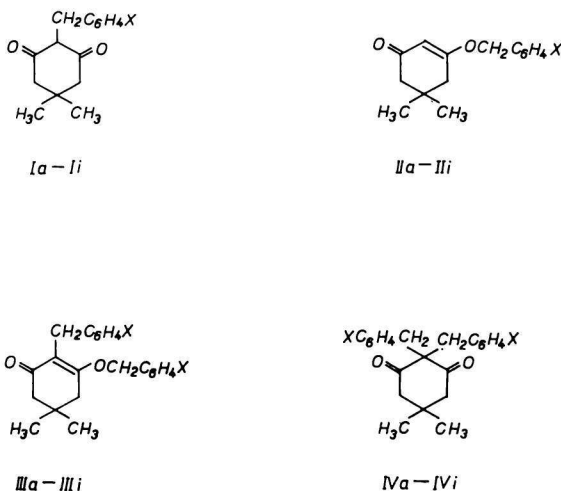
X	Yield, %				
	Total	C-derivative (I)	O-derivative (II)	C,O-derivative (III)	C,C-derivative (IV)
<i>p</i> -NO ₂	82.82	11.40	14.10	7.80	65.80
<i>m</i> -Cl	89.44	42.16	24.27	13.07	19.50
<i>p</i> -Cl	63.26	11.30	21.80	8.10	97.20
<i>p</i> -Br	60.50	26.70	23.50	6.70	42.90
H	56.61	13.90	27.70	9.70	48.60
<i>m</i> -OCH ₃	45.68	20.14	30.55	20.14	36.10
<i>p</i> -CH ₃	60.03	11.02	34.60	10.41	43.34
<i>m</i> -CH ₃	76.77	13.88	35.18	11.10	39.81
<i>p</i> -OCH ₃	59.68	—	40.65	10.44	48.89

The portion insoluble in benzene was dissolved in water (50 ml); the unchanged 5,5-dimethyl-1,3-cyclohexanedione and 2-(X-benzyl)-1,3-cyclohexanedione (*I*) precipitated after acidifying the solution with hydrochloric acid. They were separated chromatographically using chloroform—ethanol (10:1) as eluent. Analytical data are presented in Table 1, total yields as well as yields of individual substances are given in Table 2.

Results and discussion

The reactions of dimedone anion with substituted X-benzyl bromides were carried out in acetone, *i.e.* in a solvent where the reaction was assumed to proceed by the S_N2 mechanism. Anhydrous potassium carbonate was used for generation of the anion. The reactions with all benzyl bromides were carried out under the same conditions, *i.e.* at $40 \pm 1^\circ\text{C}$ and for 3 hrs which was the reaction time of the slowest reaction. Within this time the dimedone anion reacted with *p*-nitrobenzyl bromide. With the other benzyl bromides the reaction proceeded faster; the fastest reaction was with *p*-methoxybenzyl bromide. Under the applied experimental conditions all four possible derivatives were formed. The only exception was the reaction with *p*-methoxybenzyl bromide where we failed to isolate the product of C-alkylation to the first degree because this reacted rapidly with another molecule of methoxybenzyl bromide (Scheme 1).

The compounds *Ia—Ih*, 2-(X-benzyl)-5,5-dimethyl-1,3-cyclohexanediones, were the C-alkylation products; the compounds *IIa—IIIi*, 3-(X-benzyloxy)-5,5-dimethyl-2-cyclohexen-1-ones, were the O-alkylation products to the first degree; the compounds *IIIa—IIIi*, 2-(X-benzyl)-3-(X-benzyloxy)-5,5-dimethyl-2-cyclohexan-1-ones, and *IVa—IVi*, 2,2-di-(X-benzyl)-5,5-di-



Scheme 1

methy-1,3-cyclohexanediones, were the products of C,O-dibenylation and C,C-dibenylation (benzylations to the second degree). It is evident from the results of benzylations to the first degree (Table 2) that the lowest yield of O-benylation was obtained with *p*-nitrobenzyl bromide and the highest one with *p*-methoxybenzyl bromide. Of the used substituents, *p*-nitro group had the most significant electron-accepting properties and *p*-methoxy group had the most significant electron-releasing properties. The obtained results of benzylation are in agreement with the *Kornblum* rule [2] because the electron-accepting substituent acted against polarization of the C—Br bond and, consequently, the transition state of the reaction of dimedone anion with benzyl bromide was shifted to S_N2 mechanism. Inversely, the electron-releasing substituent contributed to polarization of the C—Br bond and the transition state of the reaction was shifted to S_N1 mechanism. The proportion of the O-derivative increased with the decreased values of the Hammett σ or σ^+ constants. We have found that $\log C/O$ is the function of the σ^+ values of the substituents (Fig. 1, Table 3) according to the equation

$$\log C/O = 0.381 \sigma^+ (\pm 0.05) + 0.291.$$

$$r = 0.95$$

This linear dependence was not valid for benzylation of the dimedone anion to the second degree. On benzylation with *m*-substituted benzyl bromides to the second degree, less C,C-dibenzyl derivative was formed than required for the linear dependence. This can be explained by the fact that due to the effect of substituents in *m*-position the approach to the softer nucleophilic centre was to some extent sterically hindered and, therefore, the difference between the hardness and the softness of the carbon and oxygen nucleophilic centres increased. However, when only the results obtained with *p*-substituted benzyl bromides were correlated, a linear dependence of $\log CC/CO$ on the σ^+ constants was obtained. This dependence was not evaluated in detail because we disposed of results obtained with five *p*-substituted benzyl bromides only.

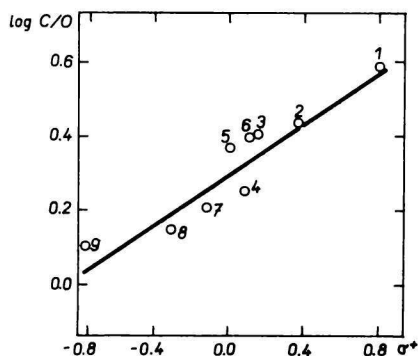


Fig. 1. Dependence of $\log C/O$ on the σ^+ constants of substituents in the reaction of dimedone anion with substituted X-benzyl bromides.

(The numbering of compounds is the same as in Table 3.)

The structures of compounds *I—IV* were determined on the basis of their i.r. and $^1\text{H-NMR}$ spectra. The compounds *Ia—Ih* in chloroform as well as in solid state appeared, similarly to dimedone, in diketo and keto enol forms. The diketo form showed two bands in the region above 1700 cm^{-1} . The band at $1708\text{—}1714\text{ cm}^{-1}$ belonged to asymmetrical and the band at $1738\text{—}1745\text{ cm}^{-1}$ to symmetrical vibrations of the carbonyl groups. The keto enol form showed a different spectrum. The band at 1650 cm^{-1} belonged to the $\text{C}=\text{O}$ group engaged in conjugation with the double $\text{C}=\text{C}$ bond which showed a band at 1620 cm^{-1} . Two bands were evident in the spectrum of the compounds *IIa—IIIi* in the region $1600\text{—}1650\text{ cm}^{-1}$; the first one belonged to $\text{C}=\text{O}$ bond (at about 1650 cm^{-1}) which was conjugated with the double bond (at about 1620 cm^{-1}). Only the compounds *IIIa—IIIi* had analogous spectra. The compounds *IVa—IVi* showed two bands corresponding to symmetrical and asymmetrical stretching vibrations of the $\text{C}=\text{O}$ group above 1700 cm^{-1} .

Table 3

Ratios C/O (reaction to the first degree) and CC/CO (reaction to the second degree) in the reaction of 5,5-dimethyl-1,3-cyclohexanedione anion with substituted X-benzyl bromides in acetone

Benzyl bromides	X	C/O	log C/O	CC/CO	log CC/CO	σ^+ , (σ)
1	<i>p</i> -NO ₂	3.84	0.59	8.40	0.92	0.80
2	<i>m</i> -Cl	2.77	0.44	1.72		0.39
3	<i>p</i> -Cl	2.53	0.41	7.03	0.80	0.15
4	<i>p</i> -Br	2.55	0.40	6.39	0.80	0.11
5	H	2.27	0.37	5.00	0.70	0.00
6	<i>m</i> -OCH ₃	1.70	0.23	1.49		0.12
7	<i>m</i> -CH ₃	1.60	0.21	3.58		-0.09
8	<i>p</i> -CH ₃	1.36	0.14	4.16	0.62	-0.31
9	<i>p</i> -OCH ₃	1.02	1.01	4.66	0.66	-0.78

Table 4

The $^1\text{H-NMR}$ spectra of the compounds *I—IV* in p.p.m. on δ scale^a

Compound	CH ₃	CH ₂ -CO	CH ₂ -C=C	O-CH ₂ -ArX	-CH-	C-CH ₂ -ArX
<i>I</i> Diketo form	1.15	2.60	—	—	2.50	3.15
Keto enol form	1.00, 0.95	2.25	2.35	—	—	3.65
<i>II</i>	1.05	2.25	2.35	4.90	5.45	—
<i>III</i>	1.0, 0.95	2.25	2.45	5.70	—	3.65
<i>IV</i>	0.25	1.96	—	—	—	3.25

a) These are the mean values from the results presented in Table 1.

The $^1\text{H-NMR}$ spectra of compounds *I—IV* were also different. With the compounds *Ia—Ih* it was possible to distinguish the diketo and the keto enol forms. The compounds *I—IV* differ mainly with regard to the bands belonging to $\text{C—CH}_2\text{—ArX}$ and $\text{O—CH}_2\text{—ArX}$ (Table 4). The differences in the $^1\text{H-NMR}$ spectra made it possible to determine compounds *II* and *III* in the mixture quantitatively. It was very advantageous because the R_F values of these compounds were very similar. As the substituent on phenyl affected the band positions of individual types of compounds only negligibly, we presented in Table 4 the mean values of band positions of compounds *I—IV*. The actual values differed from the presented ones at most by 0.05δ .

References

1. Pearson, R. and Songstag, J., *J. Amer. Chem. Soc.* **89**, 1827 (1967).
2. Kornblum, N., Smiley, R., Blackwood, R., and Iffland, D., *J. Amer. Chem. Soc.* **77**, 6269 (1953).
3. Le Noble, W. and Puerta, J., *Tetrahedron Lett.* **1966**, 1087.
4. Brieger, G. and Pelletier, W., *Tetrahedron Lett.* **1965**, 3555.
5. Kurts, A. L., Beletskaya, I. P., Masias, A., Yufit, S. S., and Reutov, O. A., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 1473.
6. Kurts, A. L., Beletskaya, I. P., Masias, A., and Reutov, O. A., *Tetrahedron Lett.* **1968**, 3679.
7. Kurts, A. L., Masias, A., Genkina, N. K., Beletskaya, I. P., and Reutov, O. A., *Dokl. Akad. Nauk SSSR* **187**, 807 (1969).
8. Cardillo, B., Casnati, G., Pochini, A., and Ricca, A., *Tetrahedron* **23**, 3771 (1967).

Translated by A. Kardošová