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STRUCTURE OF THE PRODUCTS OF THE O-MONOALKYLATION OF PYROCATECHOL BY α-BROMOKETONES

I. B. Dzvinchuk, N. V. Kuznetsov,
and M. O. Lozinskii

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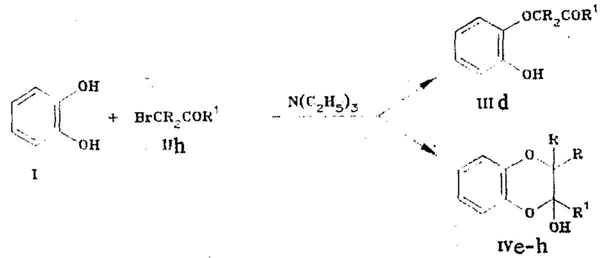
The reaction of pyrocatechol with α-bromoketones in the presence of triethylamine leads to the formation of o-hydroxyphenoxymethyl ketones or 2-hydroxy-2,3-dihydro-1,4-benzodioxines. PMR spectroscopy revealed ring–chain tautomerism of the products obtained. The relative effect of structural factors on the stability of the ring structure was evaluated.

The products of the monoalkylation of pyrocatechol I by chloroacetone [1] and phenyacyl bromide (2) were initially considered to be phenols III. Later spectroscopic studies showed that both these compounds have cyclic structure IV, while their sodium derivatives exist as the open form III [3, 4]. There have also been reports of the preparation of the acyclic structural analog of III (R = H, R^1 = $COCH_3$) and its cyclic derivatives IV [R^1 = $C(OCH_3)_2CH_3$ and $C(OCH_2)CH_3$] by an independent method [5, 6]. No data have been given for the ketol–lactol equilibrium of these compounds in solution. It was of interest to determine the preparative range of this reaction in order to elucidate the capacity of its products to under ring–chain transformations and establish the relationship of this capacity to the structure of these compounds.

The reaction was carried out with a twofold excess of diphenol I relative to the alkylating component. Triethylamine was used as the base instead of the alkaline reagents previously employed. These conditions permitted us to suppress side reactions such as 0,0'-dialkylation, oxidation, Favorskii rearrangement and dehydrobromination, simplify the synthesis procedure and enhance the yield of the O-monoalkylation product. The reaction is rather general in nature, encompassing α-bromo derivatives of aromatic, heteroaromatic and aliphatic ketones with both normal and branched hydrocarbon chains IIa-h. The structure of the starting alkylation agent has only a slight effect on the yield but determines the cyclic or acyclic structure of the final product. Thus, the reaction with bromoketones IIa-d leads to the formation of o-hydroxyphenoxymethyl ketones IIIa-d. The other bromoketones gave 2-hydroxy-2,3-dihydro-1,4-benzodioxines IVe-h.



IIa–g, IIIa–d, IVe–g R = H, IIh, IVh R = CH_3; II, IIIa R^1 = 2,4,6-$(CH_3)_3C_6H_2$, b R^1 = 2-thienyl, c R^1 = 2-furyl, d R^1 = 2,4,5-$(CH_3)_3C_6H_2$; II, IVe R^1 = C_6H_5, f R^1 = t-C_4H_9, g,h R^1 = CH_3

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TABLE 1. Characteristics of Compounds Synthesized

Compound	mp (or bp), °C [pressure, hPa]	ν, cm⁻¹		Found, %		Chemical formula	Calculated, %		Yield, %
		O—H	C=O	C	H (S)		C	H (S)	
IIIa	(230—240) [20]†	3540, sh, 3380	1715, 1700, sh	75,6	6,7	$C_{17}H_{18}O_3$	75,5	6,7	53
IIIb	111,5—112,5	3450, 3320	1670	61,3	4,5 (13,8)	$C_{12}H_{10}O_3S$	61,5	4,3 (13,7)	79
IIIc	113—113,5	3400, 3340, sh	1680	65,9	4,5	$C_{12}H_{10}O_4$	66,0	4,6	60
IIId	83,5—84,5	3195	1670	75,3	6,7	$C_{17}H_{18}O_3$	75,5	6,7	76
IVe	109—110,5‡	3440	—	73,8	5,4	$C_{14}H_{12}O_3$	73,7	5,3	58
IVf	67—68,5	3505	—	68,9	7,5	$C_{12}H_{16}O_3$	69,2	7,7	70
IVg	98—99 (130—137) [20]**	3250	—	65,0	6,2	$C_9H_{10}O_3$	65,0	6,1	58
IVh	50—51 (128—135) [20]	3435, 3400	—	67,7	7,1	$C_{11}H_{14}O_3$	68,0	7,3	53

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*IIIb and IVg recrystallized from CCl_4; IIc and IId, and IVe recrystallized from benzene, IVf and IVh recrystallized from hexane.

†n_D^{22} 1.5692.

‡Mp109.5-111°C (2.67 hPa) [4].

**Mp 100°C, bp 135-145°C hPa) [4].

The structure of the alkylation products was found relative to the presence of absence of the IR $\nu_{C=o}$ band (the characteristics of III and IV) are given in Table 1). We should note that all the isolated reaction products do not give a positive test with ethanolic $FeCl_3$ diagnostic for the phenol hydroxy group. A study of the PMR spectra of their solutions in deuteroacetone established that previously described phenyl and methyl derivatives IVe and IVg [4] exist in solution as a mixture of tautomeric ketol III and lactol (IV). The tendency to undergo ring—chain tautomeric transformations for the newly obtained compounds varies in a broad range. Within the limits of the PMR spectroscopic sensitivity, IIIa exists exclusively in the ketol form, while IVh exists exclusively in the lactol form. The solutions of the remaining compounds displayed the ketol—lactol equilibrium III $\rightleftarrows$ IV (the PMR spectral parameters are given in Table 2).

We should note that the PMR spectrum of IVg in $CDCl_3$ was given by Rosnati et al. [5]. Signals for protons of the $CH_3C{=}O$ and $CH_2C{=}O$ groups may be discerned along with the stronger signals for the protons of the cyclic form. However, these authors did not consider the protons of the cyclic form. However, these authors did not consider the question of presence of the acyclic ketol form IIIg in solution. Nevertheless, the spectrum of IVg was given as evidence for the acyclic structure of structural analog (R = H, R^1 = $COCH_3$), in whose spectrum the CH_2 group signal appears as a singlet. The assignment of structure III to this compound raises doubt since the comparison of these spectra was carried out incorrectly. Only the difference in the multiplicity of the CH_2 group signals was taken into account while the similarity of their chemical shifts was not considered. In our spectra, the signal for the diastereotopic protons of the CH_2 group of the cyclic form are not seen as a quartet for all these compounds. This signal is not split for IVc apparently as a result of a coincidental isochronicity of the methylene group protons which leads to a degenerate AB system.

In our PMR spectra, the alkyl group protons of both tautomeric forms appear separately and their assignment is not difficult. The tautomeric equilibrium constant K_T (Table 2) was found using the ratio of the integral intensities of the CH_2 group signals. Under our conditions, the tautomeric equilibrium of IIIa-d is shifted toward the open form, while it is shifted toward the ring form for IVe-h.

The structural differences in the series of tautomeric systems IIIa-g are due only to the nature of only the R^1 substituent. Steric hindrance by this substituent leads to destabilization of the ring form. A decrease in the stability of the ring form also is encountered upon substituting the aliphatic substituent by an aromatic or replacement of the aromatic substituent by a π-electron-rich heteroaromatic substituent. In this case, destabilization of this form may be attributed to the gain in the energy of the ketol form due to conjugation of the substituent with the C=O group and the decrease in the electron deficiency of the carbon atom of this group. This effect in heteroanalogs is even more pronounced as a consequence of the mesomeric interaction of the heteroatoms of the thiophene and furan ring with the carb-

TABLE 2. PMR Spectral Parameters of the Tautomeric Forms and Constants of the III $\rightleftarrows$ IV Equilibrium

Compound	R	R'	Chemical shift, δ, ppm								$K_T = \frac{[\text{lactol}]^\dagger}{[\text{ketol}]}$
			R		R'		HO		aromatic protons of the pyrocatechol fragment		
			ketol III	lactol IV*	ketol III	lactol IV	ketol III	lactol IV	ketol III	lactol IV	
IIIa	H	2,4,6-$(CH_3)_3C_6H_2$	5,00,s	—‡	2,10, s ($2CH_3$) 2,19, s (CH_3) 6,81, s (2H)	—‡	7,73, s	—‡	6,65—6,97, m	—‡	~0
IIIb	H	2-Thienyl	5,33, s	3,97; 4,22, q (1,6)	7,10—8,02, m	—‡	7,99, s	6,62, d	6,70—7,03, m	6,81, m	0,27±0,01
IIIc	H	2-Furyl	5,22, s	4,16, s	6,37—7,82, m	—‡	8,02, s	6,53, s	6,61—6,94, m	6,84, m	0,27±0,01
IIId	H	2,4,5-$(CH_3)_3C_6H_2$	5,29, s	3,88; 4,14, q (1,2)	2,18, s ($2CH_3$) 2,34, s (CH_3) 7,00, s, 7,65, s (2H)	2,13, s, 2,14, s, 2,39, s ($3CH_3$) 6,90, s 7,43, s (2H)	8,05, s	6,00, s	6,63—6,95, m	6,80, m	0,36±0,02
IVe	H	C_6H_5	5,41, s	3,79; 4,07, q (1,5)	7,29—7,42; 7,86—7,89, m	7,25—7,29; 7,86—7,89	7,89, s	6,14, d	6,55—6,88, m	6,80, m	4,22±0,14
IVf	H	$C(CH_3)_3$	5,02, s	3,92; 4,16, q (1,2)	1,13, s	1,05, s	7,92, s	5,16, d	6,60—6,92, m	6,73, m	7,72±0,31
IVg	H	CH_3	4,70, s	3,81; 3,98, q (0,9)	2,13, s	1,45, s	8,11, s	5,71, d	—‡	6,74, m	31,9±1,2
IVh	CH_3	CH_3	—‡	1,20, s; 1,35, s	—‡	1,45, s	—‡	5,45, s	—‡	6,71, m	>99

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*For all the AB quartet systems, J = 11 Hz; the J value (Hz) is given for the coupling between one of the protons of the CH_AH_B group and the proton of the lactol OH group in parentheses.

†K_T ~ 0 if the lactol form is not observed and K_T > 99 if the ketol form is not observed.

‡Signal not discerned.

onyl group. This interaction for the furyl derivative is less effective due to the great electronegativity of the ring heteroatom (see the review by Joule and Smith [7], p. 214) and the stability of the ring form for this derivative should likely be greater than for the thiophene analog. However, a difference between these compounds within the sensitivity range for the method used to determine the tautomeric composition could not be detected. The substituent at the C=O group in ketol—lactol systems with similar structure analogously affects the stability of the ring form (see the work of Valter [8], pp. 173, 177-178 and the later review by Valter [9], pp. 1376-1383).

The shielding of the keto group in the α-position of the ring formed by methyl substituents usually leads to destabilization of the ring form [8, p. 181; 9, p. 1383]. However, the introduction of methyl groups into a unit already containing a conformationally rigid pyrocatechol fragment probably sharply limits the freeedom of rotation of the open form and provides for spactial approximation of the C=O and HO groups. Such consequences in ring—chain tautomeric systems lead to stabilization of the ring form [8, pp. 178-180; 9, pp. 1383-1392].

The electronic effect of the ethereal oxygen atom of ketol forms III on both reaction sites apparently provides an additional contribution to stabilize the ring forms IV. The inductive electron-withdrawing effect enhances the electron deficiency of the C=O carbon atom and, thus, its tendency to add a phenol hydroxyl. The latter, in turn, should have a marked tendency to add to a C=O group due to the mesomeric electron-donor effect of the ortho ethereal oxygen atom.

Thus, the products of the O-monoalkylation of pyrocatechol by α-bromoketones have a marked tendency to form the lactol structure. However, substituents which have a significant electron-donor or shielding effect on the C=O group may provide stabilization of the ketol form.

EXPERIMENTAL

The purity of III and IV was monitored by thin-layer chromatography on Silufol UV-254 plates using 2:1 chloroform—CCl_4 as the eluent. The IR spectra were taken on a UR-20 spectrometer neat on KBr plates for IIIa and IVh and in KBr pellets for the other compounds. The PMR spectra were taken on a Bruker WP-200 Fourier pulse spectrometer at 200 MHz in $(CD_3)_2CO$ with HMDS as the internal standard. The 0.3 mole/liter solutions were maintained at constant 25°C for 24 h prior to taking the spectra. The position of the tautomeric equilibrium did not change upon maintenance up to 14 days. The K_T equilibrium constants were calculated taking account of the relative of the error in measuring the integral intensities of the diagnostic signals.

o-Hydroxyphenoxymethyl Ketones III or 2-Hydroxy-2,3-dihydro-1,4-benzodioxines IV (Table 1). A mixture of 22 g (0.2 mole) I, 0.1 mole bromoketone II and 15.1 ml (0.11 mole) triethylamine in 30 ml 2-propanol was heated at reflux using a condenser equipped with a liquid seal for 2 h (10 and 4 h for IIa and II h, respectively). The reaction mixture was cooled, diluted with 50 ml water, acidified with 15 ml concentrated hydrochloric acid and left overnight. The crystallized products were filtered off, washed with water and dried. Prior to distillation, IVg and IVh were distilled in vacuum. The reaction mixture was extracted with 100 ml ether in order to separate IIIa. The extract was washed with two 100-ml portions of water. The reaction product was extracted with three 50-ml portions of aqueous KOH. The alkaline solution was immediately acidified with 40 ml concentrated hydrochloric acid. The oil separated was extracted with 100 ml chloroform. The extract was washed with three 100-ml portions of water, dried over calcium chloride and passed twice through a 10-cm alumina column using chloroform as the eluent. The solvent was evaporated and the residue was distilled in vacuum.

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