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Allylic Bromination of Compounds of the Cyclohexene Series

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Compounds of the cyclohexene series, synthesized by the Diels–Alder reaction, are readily accessible and diverse. It seemed of interest to us to begin a systematic study of the allylic bromination reaction of these compounds by means of N-bromosuccinimide. Such a choice of objects of investigation is explained primarily by the fact that, by bromination and subsequent dehydrobromination, it is possible to effect the transition from accessible adducts of diene condensation to the corresponding cyclohexadienes, using the latter for the synthesis of natural substances and related compounds. On the other hand, the study of substitution reactions of mobile allylic bromine would greatly facilitate the problem of synthesizing compounds of the cyclohexane series containing various functional groups.

As the first representative of compounds of the cyclohexene series, aldehyde (III) was taken; here it should be noted that the action of N-bromosuccinimide on unsaturated aldehydes has in general been studied hardly at all ($^{1-3}$). Bromination of aldehyde (III) was carried out in a solution of boiling carbon tetrachloride in the presence of benzoyl peroxide. The reaction product—bromoaldehyde (IV)—is extremely unstable and prone to spontaneous elimination of HBr.

Of the chemical transformations of bromoaldehyde (IV), the reaction of its dehydrobromination under the action of various agents was studied in greatest detail. As a result of dehydrobromination, mixtures of substances are always formed, the separation of which was carried out by chromatography and crystallization of semicarbazones and 2,4-dinitrophenylhydrazones.

Heating bromoaldehyde (IV) with quinoline on a boiling water bath gives only an insignificant amount of the expected cyclohexadiene aldehyde (VI); the greater part of the latter undergoes further dehydrogenation with formation of *o*-tolualdehyde (VII). On dehydrobromination of bromoacetal (VIII) with silver oxide (anhydrous benzene, shaking for 70 hours at 20° in an N_2 atmosphere) and subsequent hydrolysis, the main reaction product is likewise *o*-tolualdehyde (VII). Along with this compound, tetraoxymethylcyclohexane aldehyde (X), formed upon hydrolysis of diepoxyacetal (IX), was isolated as the 2,4-dinitrophenylhydrazone; the structure of (X) was confirmed by reaction scheme: compounds I–X, including conversion of III to IV with NBS; formation of V with CH3OH + NaOH; dehydrobromination of IV to VI/VII with Et3N or quinoline; conversion of III to VIII via CH(OEt)3 then NBS; conversion VIII to IX with Ag2O, IX to X with H2O; and hydrolysis/aromatization pathways

Figure 1: reaction scheme: compounds I–X, including conversion of III to IV with NBS; formation of V with CH3OH + NaOH; dehydrobromination of IV to VI/VII with Et3N or quinoline; conversion of III to VIII via CH(OEt)3 then NBS; conversion VIII to IX with Ag2O, IX to X with H2O; and hydrolysis/aromatization pathways

its IR spectrum. However, under milder conditions of dehydrobromination of bromoaldehyde (IV) (boiling with an alcoholic solution of triethylamine), preferential formation of cyclohexadiene aldehyde (VI) takes place; whereas *o*-tolualdehyde (VII) is obtained only in small amount. In addition, bromoaldehyde (IV) was converted into methoxycyclohexene aldehyde (V) by interaction with a methanolic solution of caustic potash.

In contrast to unsaturated aldehydes, the reaction of N-bromosuccinimide with unsaturated ketones (^{4,5}), including β-ionone ($^{6-8}$), has been widely described in the literature. The Δ^3-cyclohexene ketone (XII) studied by us, which is an analogue of β-ionone, is smoothly brominated by N-bromosuccinimide—

with difficulty, giving only an unstable bromo derivative of probable structure (XIII), which could not be isolated in pure form. In contrast to bromocyclohexene aldehyde (IV), bromoketone (XIII), under the action of various dehydrobrominating agents (diethylaniline, triethylamine, alcoholic alkali solution, silver oxide, sodium acetate), forms only one substance—an alkylaromatic ketone (XV). Evidently, in this case the initial reaction product—the cyclohexadienone ketone (XIV)—is readily aromatized as a result of isomerization of the double bond from the side chain into the ring. It should be noted that the analogous bromo derivative of β-ionone, under the action of dimethylaniline at 80° or of silver oxide at room temperature, gives a quite stable cyclohexadienone analog of β-ionone (7,8). This stability of the latter is due to the fact that, for its further aromatization, migration of one of the gem-methyl groups is necessary; and indeed, under more severe dehydrobromination conditions (boiling dimethylamine), an alkylaromatic ketone (6,8) was obtained, similar in structure to ketone (XV). To prove the structure of ketone (XV), its independent synthesis was carried out according to the scheme: (III)→(XVI)→(XVII)→(XV).

The structures of the aldehydes and ketones obtained by us were confirmed by studying the UV absorption spectra of their 2,4-dinitrophenylhydrazones; at the same time, we sought to reveal the dependence of the light absorption of the compounds studied on their structure. To obtain comparative charac-

Table 1

reaction scheme: compound XII to XIII with NBS; XIII to XIV by —HBr; XIV to XV; III to XI with CH3COCH3 (NaOH), XI to XII with KHSO4 (140°); III to XVI with S at 180°; XVI to XVII with 1) CH3COCH3 (NaOH), 2) KHSO4 (140°); XVII to XV with H2, Pd/SrCO3

Figure 2: reaction scheme: compound XII to XIII with NBS; XIII to XIV by —HBr; XIV to XV; III to XI with CH3COCH3 (NaOH), XI to XII with KHSO4 (140°); III to XVI with S at 180°; XVI to XVII with 1) CH3COCH3 (NaOH), 2) KHSO4 (140°); XVII to XV with H2, Pd/SrCO3

Compounds	B.p., °C/mm	M.p., °C	Refractive indices	Found, % C	Found, % H	Found, % Br	Calculated, % C	Calculated, % H	Calculated, % Br	λ max
IV	125/0,2 (bath)		n_D^{19} 1,5345	48,10	5,69	37,10	47,29	5,42	39,41	
V	77—79/12		n_D^{23} 1,4664	70,21	9,08		70,13	9,09		226362
DNPH *		132—135								
VI DNPH		140—142		54,06	5,08		54,02	4,82		222361—363
VII DNPH		193—194		56,08	4,40		56,00	4,00		220—221378—384
VIII	100—120/0,4 (bath)		n_D^{25} 1,5075			23,94			28,88	
X DNPH		121,5—123		45,77	4,35		45,40	4,86		
XI	124—125/4	84—86	n_D^{17} 1,4934	72,43	10,07		72,53	9,89		
XII	98—99/3,5		n_D^{18} 1,4985	80,36	9,75		80,48	9,75		
DNPH		144—146		59,32	5,90		59,30	5,81		252375—377
XV	85—86/1		n_D^{16} 1,5138	81,50	8,77		81,48	8,64		
DNPH		137,5—138,5		59,45	5,40		59,65	5,26		362
XVII	106,5/0,5		$n_D^{17,5}$ 1,5289	82,80	7,71		82,50	7,50		

Compounds	B.p., °C/mm	M.p., °C	Refractive indices	Found, % C	Found, % H	Found, % Br	Calculated, % C	Calculated, % H	Calculated, % Br	λ, max
DNPH		223—224		60,16	4,77		60,00	4,71		230 300 380—388
XVIII	87/14		$n_D^{15}1,4568$	70,89	10,68		70,59	10,59		
XIX	58/13		$n_D^{19}1,4480$	76,17	10,92		76,18	11,11		
DNPH		152—153,5								229 360—361
XX	95/4		$n_D^{14,5}1,4984$	79,31	10,94		79,52	10,84		
DNPH		143,5—145		58,80	6,37		58,96	6,35		251 377
XXI	108/12		$n_D^{18}1,4610$	78,35	12,01		78,57	11,90		
DNPH		109—111,5		58,74	7,05		58,62	6,89		228 361
XXXIII										
DNPH		174—176								254 378—379
XXXIV										
DNPH		189—190								257 384—385
XXV										
DNPH		193—194								230—232 306 389
XXVIII	80—82/0,12		$n_D^{21}1,5134$	45,90	5,90	34,33	46,35	5,58	34,33	
XXVII	101—102/0,5		$n_D^{20}1,5322$	47,94	5,28	39,60	48,00	5,00	40,00	
XXIX	90,5—91,5/14		$n_D^{25}1,4960$	71,21	8,05		71,05	7,89		
XXXI		274—275		58,62	6,98		58,69	6,52		

* DNPH: 2,4-dinitrophenylhydrazone.

characteristics of light absorption, in addition to those already available, a series of hydroaromatic aldehydes (XIX, XXIII, XXIV) and ketones (XX, XXI, XXV) of varying degrees of unsaturation and with different positions of the double bonds in the molecule was synthesized.

The absorption curves obtained by us and the regularities found in the mutual arrangement of the absorption maxima of 2,4-dinitrophenylhydrazones are in agreement with the generalizations already available in the literature.

assumptions concerning the dependence of the light absorption of 2,4-dinitrophenylhydrazones on the structure of the starting carbonyl compounds (^{9}).

[Reaction scheme: compounds XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, and XXV; reagents shown include 1) H_2, Pd/$CaCO_3$; 2) 20% H_2SO_4; Br_2; −HBr; 1) CH_3COCH_3 (NaOH); 2) $KHSO_4$ (140°); and H_2, Pd/$CaCO_3$.]

Finally, the action of N-bromosuccinimide on 2-methyl-Δ^3-cyclohexenecarboxylic acid (XXVIIa), its methyl ester (XXVIIb), and nitrile (XXVIIc) was studied. It was shown that bromination of compounds (XXVIIa)−(XXVIIc) proceeds smoothly in boiling carbon tetrachloride, giving the corresponding bromo derivatives (XXVIIIa)−(XXVIIIc) in good yield. It should be noted that, in the example of the methyl ester of the acid (XXVIIIb), the direction of bromination by N-bromosuccinimide into position 5 was proved by replacing the allylic bromine with a cyano group by means of cuprous cyanide; hydrolysis of the compound thus formed (XXX) led to the trans-6-methyl-Δ-tetrahydroisophthalic acid (XXXI) described in the literature (^{10}).

[Reaction scheme: compound XXVII treated with NBS gives XXVIII, which on treatment with Et_3N gives XXIX; XXVIII reacts with $Cu_2(CN)_2$ to give XXX, which on hydrolysis with alcoholic NaOH at 80° gives XXXI. A diene condensation precursor is also shown leading to XXVII.]

where
XXVI: a) R=$COOCH_3$; b) R=CN
XXVII: a) R=COOH; b) R=$COOCH_3$; c) R=CN
XXVIII: a) R=COOH; b) R=$COOCH_3$; c) R=CN
XXIX: R=$COOCH_3$
XXX: R=$COOCH_3$

In contrast to the other bromo derivatives considered above, whose dehydrobromination does not lead to the preferential formation of a cyclohexadiene system, ester (XXVIIIb) is dehydrobrominated to the corresponding cyclohexadiene derivative in a sufficiently good yield. Thus, by bromination and dehydrobromination of ester (XXVIIb), it is possible to pass easily from compounds of the Δ^3-cyclohexene series, obtained as a result of diene condensation, to compounds of the cyclohexadiene series. On the basis of the latter, the possibility opens for the synthesis of cycloaliphatic polyenes close in structure to natural ones.

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