REACTION OF 1-BROMO-1,2-PENTADIEN-4-ONE WITH SOME NUCLEOPHILES

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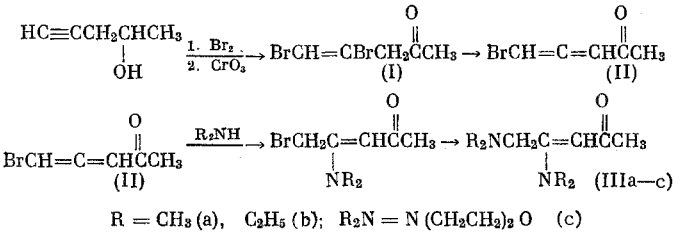
The nucleophilic addition reaction of amines and alcohols to the esters of the 4-bromo-2,3-butadienoic [1, 2] and 2-chloro-2,3-butadienoic [3] acids proceeds easily, with a fixation of the nucleophile to the central carbon atom of the allene grouping. In the present paper we report some rules for the behavior of still another allene of this type, namely 1-bromo-1,2-pentadien-4-one (II), which was obtained from 1-pentyn-4-ol [4]:



As was already mentioned earlier [2], a sequence of transformations apparently takes place when ketone (II) is reacted with amines: addition of the amine to the allene grouping, with subsequent replacement of the formed allylic halide by the amine. The addition products of primary amines (benzyl-, butyl-, and methylamine) could not be isolated. In the case of secondary amines (dimethylamine, diethylamine, morpholine) the corresponding diaminovinyl ketones of the (III) type were obtained, which are apparently formed as one trans-isomer, which is indicated by the absence of an allylic spin–spin coupling constant [5] in the NMR spectra of these compounds. In their UV spectra an intense absorption maximum is found at 320 nm (Table 1), which is characteristic for aminovinyl ketones [6].

When bromoallene (II) is reacted with CH_3OH in the presence of CH_3ONa, even under mild conditions (–40°C), addition of the alcohol takes place with the formation of methyl 2-methoxy-3-bromoallyl ketone (IV). In the case of other alcohols the products of a similar "direct" nucleophilic addition could not be isolated, since their amount in the mixture (based on the data of the NMR spectra) proved to be insignificant. The main products of this reaction proved to be the corresponding esters of levulinic acid (VIIIa, b),

TABLE 1. Analytical and Spectral Data for (III) Compounds

Compound	Yield, %	NMR spectrum in CCl_4, ppm			$\nu_{NC=CHCO}$, cm^{-1}	UV spectrum in alcohol		n_D^{20}	N, %	
		δ_{CH_3CO}	δ_{CH_2N}	$\delta_{CH=}$		λ_{max}	ε		found	calculated
(IIIa)	36	1,9	3,64	4,80	1650, 1560	318	19600	1,5312	—	—
(IIIb)	43	1,87	3,83	4,95	1650, 1540	321	22300	1,5222	11,86	12,38
(IIIc)	49	1,88	3,72	4,96	1655, 1550	319	21800	—*	11,21	11,02

*Mp 88-89° (from a hexane–ethyl acetate mixture).

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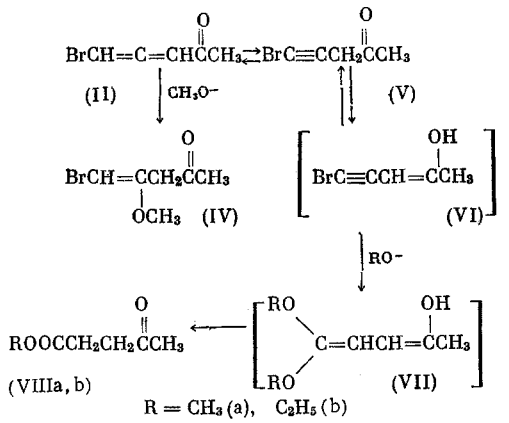
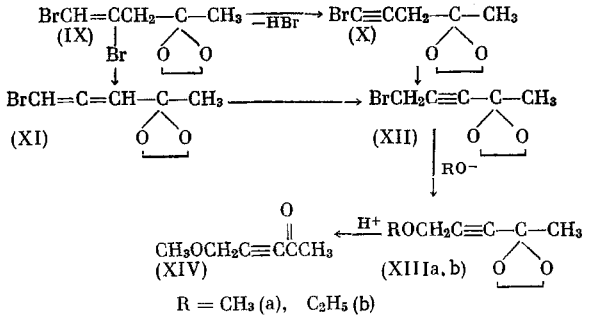
which were isolated as the 2,4-dinitrophenylhydrazones. The same mixture of products (IV) and (VIII) is also formed when dibromo ketone (I), which is a precursor of (II), is treated directly with the alcoholates of alcohols:



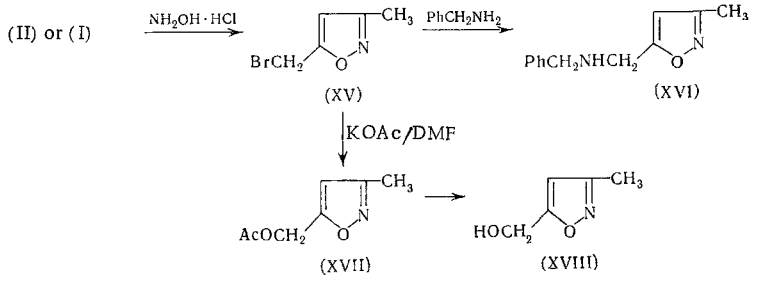
The predominant formation of levulinic acid esters is probably due to the high activity of the enol form (VI) of the isomeric bromoacetylenic ketone (V), from which intermediate products of the (VII) type can be formed as the result of the successive reactions of nucleophilic substitution and addition, which products give the esters (VIIIa, b) on hydrolysis, which does not contradict the concepts regarding the mechanism of the transformations of analogous systems [7].

Products of a different type, and specifically the ethylene ketals of a 1-alkoxy-2-pentyn-4-one (XIII) were obtained from ethylene ketal (IX) when it was refluxed with alcoholates in either alcohol or DMSO [8]. The structure of the (XIII) ketals followed from the spectral data, the elemental analysis, and hydrolysis to the corresponding ketone (XIV):



In the given case the initially formed bromo ketals of either the acetylenic (X) or the allenic (XI) type undergo isomerization under the influence of bases to bromo ketals of the propargyl type (XII), which then give the corresponding ethylene ketals of the 1-alkoxy-2-pentyn-4-one (XIII) when reacted with alcohols.

Further, ketone (II) is capable of reacting with NH_2OH to give 3-methyl-5-bromomethylisoxazole (XV), which can also be obtained by the direct reaction of dibromoketone (I) with excess NH_2OH:



The formed bromoisoxazole (XV) proved to be unstable and could not be isolated in the pure state. However, (XV) reacts easily with benzylamine and potassium acetate to give the corresponding stable derivatives (XVI) and (XVII). The saponification of acetate (XVII) gave alcohol (XVIII), which was characterized as the known p-nitrobenzoate [9], which corroborates the structure of compounds (XV)-(XVIII) as being isoxazole derivatives with functional substituents in the 5-position.

EXPERIMENTAL METHOD

The GLC determinations were carried out on a "Khrom-31" chromatograph using a glass column filled with 10% Silicone SE-30 deposited on silanized Chromosorb W. The IR spectra were taken on a UR-20 instrument, while the NMR spectra (δ, ppm) were taken on a Varian HA-60-IL instrument (internal standard = HMDS).

The 1,2-dibromo-1-penten-4-one (I) was obtained in 80-90% yield by the oxidation of 1,2-dibromo-1-penten-4-ol with a solution of sodium dichromate in ether [10]. 1-Bromo-1,2-pentadien-4-one (II) was obtained from (I) by treatment with Et_3N in ether solution [5].

1,2-Dibromo-1-penten-4-one Ethylene Ketal (IX). A solution of 26 g of (I) and 30 g of ethylene glycol in 300 ml of C_6H_6, in the presence of 0.5 g of p-toluenesulfonic acid, was refluxed in a flask fitted with a water separator for 7 h. After the usual workup and distillation we obtained 74 g (77% yield) of (IX), contaminated with 3-5% of 1,2-dibromo-1-penten-4-ol, with bp 80-84° (0.4 mm); n_D^{20} 1.5329. NMR spectrum in CCl_4: 1.32 (CH_3C ), 2.82 (CH_2C ), 3.8 (OCH_2CH_2O), 6.43 (BrCH=). Found: Br 59.64%. $C_7H_{10}O_2Br_2$. Calculated: Br 59.12%.

Reaction of 1-Bromo-1,2-pentadien-4-one (II) with Secondary Amines. To a solution of (II), obtained from 5 g of (I), in 70 ml of ether at 8-12° was added in drops 0.06 M of the appropriate amine, and the mixture was kept at ~20° for 10-12 h. The ether layer was washed with water and then dried over BaO. Vacuum-distillation (0.1 mm) gave the corresponding diamino ketones (III), the characteristics of which are given in Table 1.

Reaction of Bromo Ketones (I) and (II) with Alcohols. To a solution of 12.1 g of dibromo ketone in 30 ml of CH_3OH was added in drops, at −40°, 40 ml of a 2% solution of CH_3ONa (from 0.04 g-equiv of Na) in CH_3OH. The mixture was heated to 0°, decomposed with dry NH_4Cl, the methanol was vacuum-distilled, and the residue was extracted with ether (4 × 25 ml) and then dried over $CaCl_2$. Distillation of the residue (9.5 g) in vacuo gave 3.2 g of product with bp 25-32° (0.2 mm); n_D^{22} 1.4608-1.4706. The product is unstable when stored and, based on the data of GLC and the NMR spectrum, contains a mixture of (IV) and (VIIIa) in a ratio of ~ 1:3. Infrared spectrum: broad band at 1720 cm^{-1}. NMR spectrum of (IV) in CCl_4: 1.96 (CH_3CO), 3.68 (CH_3O), 5.64 (BrCH=), the signal of the CH_2 group is masked by the multiplet of the CH_2 group of ester (VIIIa); for (VIIIa); 2.01 (CH_3CO), 2.2-2.7 (group of lines of A_2B_2 system, $ROOCCH_2CH_2CO$), 3.5 (OCH_3). Treatment with a solution of 2,4-dinitrophenylhydrazine gave the hydrazone of the methyl ester of levulinic acid (VIIIa) with mp 140-140.5° (from alcohol).

The same mixture of products was obtained when CH_3ONa in methanol solution was reacted with the bromo ketone (II) that had been prepared in advance from 12.1 g of (I) in absolute ether; yield 25-35%.

The reaction of C_2H_5ONa in alcohol solution with bromo ketone (II) was run in a similar manner. After the above indicated workup we isolated the 2,4-dinitrophenylhydrazone of the ethyl ester of levulinic acid (VIIIb), mp 99.5-100° (from CH_3OH). NMR spectrum in $(CD_3)_2CO$: 1.12 (triplet, J = 7 Hz, CH_3C), 2.05 (CH_3C=), 2.65 (group of lines of A_2B_2 system, $ROOCCH_2CH_2C$=), 4.03 (quartet, J = 7 Hz, CH_2O), 7.83 (doublet, J = 10 Hz, 1H), 8.28 (double doublet, J = 10 and 3 Hz, 1H), 8.86 (doublet, J = 3 Hz, 1H). Found: C 47.92; H 5.08; N 17.46%. $C_{13}H_{16}N_4O_4$. Calculated: C 48.15; H 4.97; N 17.28%.

Reaction of Dibromo Ethylene Ketal (IX) with Alcoholates. To a solution of the alcoholate (from 0.03 g-atom of Na) in 60 ml of the appropriate alcohol was added 0.01 M of (IX) and the mixture was refluxed for 8-14 h, checking the completeness of reaction by the GLC data. The solvent was vacuum-distilled, and the residue was diluted with water and then extracted with ether. Distillation gave (XIII).

a) The ethylene ketal (XIIIa) obtained in this manner is contaminated with 10% of (X) and unidentified compounds; yield 55%; bp 78-81° (8 mm); n_D^{20} 1.4546. NMR spectrum in CCl_4: 1.51 (CH_3C ), 3.2 (CH_3O), 3.84 (broad singlet, OCH_2CH_2O), 3.93 (OCH_2). A solution of 4.8 g of ketal (XIIIa) in 50 ml of acetone was refluxed in the presence of 0.1 g of p-toluenesulfonic acid for 3 h. After the usual workup and distillation we obtained 2.4 g (70%) of (XIV) with bp 57° (7 mm); n_D^{22} 1.4486. Infrared spectrum (ν, cm^{-1}): 2210 (−C≡C−), 1682 (≡CCO). NMR spectrum in CCl_4: 2.3 (CH_3CO), 3.36 (OCH_3), 4.22 ($OCH_2C\equiv$). The 2,4-dinitrophenylhydrazone was obtained by treating (XIV) or directly (XIIIa) with a solution of the hydrazine in 2 N HCl

solution, mp 94-95° (from alcohol). The IR spectrum exhibits absorption at 2210 cm^{-1} (–C≡C–). Found: C 48.98; H 4.15; N 19.39%. $C_{12}H_{12}O_5N_4$. Calculated: C 49.31; H 4.14; N 19.17%.

b) The obtained ethylene ketal (XIIIb) contains ~15% of unidentified impurities; yield 42%; bp 50-55° (0.4 mm); n_D^{18} 1.4532. NMR spectrum in CCl_4 (taken on a JM-4H-100 instrument at 100 MHz): 1.09 (triplet, J = 7.5 Hz, CH_3CH_2), 1.52 (CH_3C ), 3.42 (quartet, J = 7.6 Hz, OCH_2), 3.72-3.94 (diffuse and masked by a part of the A_2B_2 system, OCH_2CH_2O), 4.0 ($OCH_2C\equiv$). 2,4-Dinitrophenylhydrazone from (XIIIb), mp 95-96° (from alcohol). There is IR absorption at 2210 cm^{-1} (–C≡C–). Found: C 50.94; H 4.49; N 18.29%. $C_{13}H_{14}O_5N_4$. Calculated: C 50.98; H 4.61; N 18.29%.

3-Methyl-5-bromomethylisoxazole (XV). A mixture of 6.6 g of $NH_2OH \cdot HCl$ in 50 ml of MeOH and 6 ml of water and 9.2 g of (I) was left to stand for 48 h, after which the solvent was vacuum-distilled, and the residue was diluted with 25 ml of water, extracted with ether, washed in succession with dilute $NaHCO_3$ and HCl solutions, and dried over $CaCl_2$. Distillation gave 3.2 g of a fraction with bp 64-76° (0.4 mm) and n_D^{19} 1.5152, which, based on the data of GLC and the NMR spectrum, contained 80% of (XV). The compound is unstable and could not be purified by distillation. NMR spectrum in CCl_4: 2.17 ($CH_3C=$), 4.35 (CH_2Br), 6.01 (CH=).

3-Methyl-5-benzylaminoisoxazole (XVI). To a solution of 4.2 g of crude (XV) in 50 ml of ether was added 4.5 g of benzylamine and the mixture was heated at 30° for 2 h. The ether layer was washed in succession with water and 2 N HCl solution. The acid extract was saturated with K_2CO_3, extracted with ether, and dried over K_2CO_3. Distillation from a flask with a little collar [140-160° (0.4 mm)] gave 2.9 g of (XVI) as an oil; n_D^{18} 1.5512. NMR spectrum in CD_3OD: 2.13 ($CH_3C=$), 3.67 (4H, CH_2N), 6.0 (CH=), 7.23 (C_6H_5). Hydrochloride, mp 233-235° (decompn.) (from absolute DMF). Found: C 60.12; H 6.30; Cl 14.60; N 11.56%. $C_{12}H_{15}ClN_2O$. Calculated: C 60.37; H 6.34; Cl 14.85; N 11.73%.

3-Methyl-5-acetoxymethylisoxazole (XVII). A suspension of 4.5 g of crude (XV) and 4.0 g of AcOK in 40 ml of DMF was heated at 50° for 2 h. The mixture was diluted with water, extracted with ether, and dried over $MgSO_4$. Fractional distillation gave 1.8 g of (XVII) with bp 80-82° (0.4 mm); n_D^{20} 1.4742. NMR spectrum in CCl_4: 1.97 (CH_3CO), 2.16 ($CH_3C=$), 4.92 (CH_2O), 5.96 (CH=). Found: N 8.91%. $C_7H_9O_3N$. Calculated: N 9.03%. Saponification of acetate (XVII) with 2% alcoholic KOH solution (15 min at 10°) gave (XVIII), bp 76-78° (0.4 mm); n_D^{19} 1.4772. NMR spectrum in CCl_4: 2.11 ($CH_3C=$), 4.48 (CH_2O), 4.8 (OH), 5.93 (CH=); p-nitrobenzoate, mp 81.5° (from alcohol), cf. [9].

CONCLUSIONS

1. 3,4-Diaminovinyl ketones are formed when 1-bromo-1,2-pentadien-4-one is reacted with secondary amines, whereas reaction with alcohols leads to the predominant formation of the esters of levulinic acid.

2. A new route was proposed for preparing the ketals of 1-alkoxy-2-pentyn-4-one and substituted 3-methylisoxazole derivatives.

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