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OXIRANYL-β-AMINOVINYL KETONES.

2.* SYNTHESIS OF 3(2H)-FURANONES

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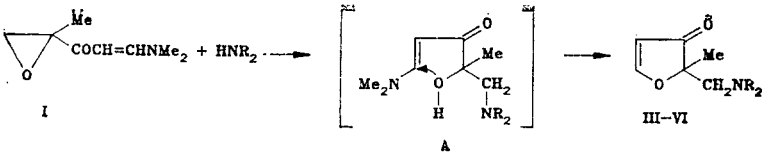
The reaction of oxiranyl-β-dimethylaminovinyl ketones with secondary amines, hydrochloric, and hydrobromic acids leads to the formation of the corresponding 2-aminomethyl- and 2-halomethyl-3-(2H)-furanones.

The 3(2H)-furanone ring is found as a structural fragment of several natural compounds [2-6]. One of the few methods available for the synthesis of 3(2H)-furanones consists in the intramolecular cyclization of γ-hydroxy-β-aminovinyl ketones [6-8] and α'-bromo- [9] or α'-hydroxy-β-aminovinyl ketones [10, 11]. In many cases, opening of the epoxide ring of epoxyketones by nucleophilic or electrophilic reagents leads to the formation of substituted α-hydroxyketones. Hence it might be expected that the opening of the epoxide ring of oxiranyl-β-aminovinyl ketones, leading to the formation of a hydroxyketone fragment, would be accompanied by intramolecular cyclization to the corresponding 3(2H)-furanones. It has, in fact, been shown that in the reaction of 1-dimethylamino-4-methyl-4,5-epoxy-1-penten-3-one (I) with dimethyl- and diethylamine, piperidine, and morpholine, the products of the opening of the epoxide ring cyclize under the conditions of the reaction of 2-aminomethyl-3(2H)-furanones III-VI in yields of 31-54%. The cyclization of the intermediate A apparently takes place via the Michael addition of the hydroxyl group to the double bond of the aminovinyl ketone with subsequent splitting off of dimethylamine and the formation of the 3(2H)-furanone.



III R=Me; IV R=Et; V R—R=$(CH_2)_5$; VI R—R=$(CH_2)_2O(CH_2)_2$

Cyclization of α'-hydroxy-β-aminovinyl ketones to 3(2H)-furanones is generally carried out in an acid medium [10, 11]. In the present case, acidification of the reaction mixture after the disappearance of the oxiranyl-β-dimethylaminovinyl ketone (TLC) did not result in any increase in the yield of 3(2H)-furanones III-VI. At the same time, 1-dimethylamino-4-methyl-4,5-epoxy-1-hexen-3-one (II), containing an epoxide ring which is less reactive with respect to amines, when reacted with morpholine did not form the corresponding furanone,

*For Communication 1, see [1].

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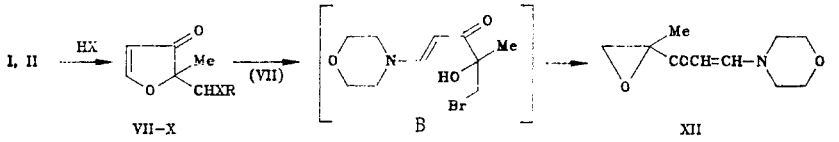
TABLE 1. Characteristics of Compounds III-X

Compound	bp (mm Hg) or mp, °C	n_D^{20}	ν, cm^{-1}		PMR spectra, δ, ppm	Found, %			Formula	Calculated, %			Yield, %
			C=C	C=O		C	H	N (Hal)		C	H	N (Hal)	
III	75...78 (2)	1,4728	1560	1705	1,13 (s, 3H); 2,08 (s, 6H); 2,28 (s, 2H); 5,37 (d, 1H); 7,93 (d, 1H)	61,7	8,2	9,2	$C_8H_{13}NO_2$	61,9	8,4	9,0	31
IV	83...85 (1)	1,4810	1570	1705	0,77 (t,6H); 1,08 (s, 3H); 2,33 (q, 4H); 2,45 (s, 2H); 5,36 (d, 1H); 7,87 (d, 1H)	65,2	9,1	7,5	$C_{10}H_{17}NO_2$	65,5	9,4	7,6	48
V	18...19	—	1570	1705	1,13 (s,3H); 1,15...1,50 (m,6H); 2,10...2,50 (m, 4H); 2,33 (s, 2H); 5,36 (d, 1H); 7,93 (d, 1H)	67,4	8,8	7,0	$C_{11}H_{17}NO_2$	67,6	8,7	7,1	54
VI	55...56	—	1560	1705	1,15 (s, 3H); 2,10...2,46 (m, 4H); 2,40 (s, 2H); 3,06...3,66 (m, 4H); 5,40 (d, 1H); 7,96 (d, 1H)	61,0	7,7	7,2	$C_{10}H_{15}NO_3$	60,8	7,6	7,1	47
VII	55...57 (1)	1,4956	1570	1710	1,33 (s, 3H); 3,51 (s, 2H); 5,55 (d, 1H); 8,10 (d, 1H)	49,0	4,7	(23,7)	$C_6H_7ClO_2$	49,2	4,8	(24,1)	56
VIII	59...61 (1)	1,5218	1560	1705	1,40 (s, 3H); 3,40 (s, 2H); 5,51 (d, 1H); 8,08 (d, 1H)	37,4	3,3	(41,4)	$C_6H_7BrO_2$	37,7	3,6	(41,8)	54
IX	67...68 (1)	1,4912	1565	1710	1,26 (d, 3H); 1,36 (s, 3H); 4,00 (q, 1H); 5,45 (d, 1H); 8,06 (d, 1H)	52,7	5,7	(21,8)	$C_7H_9ClO_2$	52,4	5,6	(22,1)	45
X	73...75 (1)	1,5120	1565	1705	1,38 (s, 3H); 1,46 (d, 3H); 4,10 (q, 1H); 5,50 (d, 1H); 8,06 (d, 1H)	40,8	4,1	(40,3)	$C_7H_9BrO_2$	41,0	4,4	(40,0)	41

probably for steric reasons. The main product of the prolonged heating of the oxiranyl ketone II with morpholine in isopropanol – (E)-4-methyl-1,5-dimorpholino-4-hydroxy-1-hexen-3-one – is the result of two processes: opening of the oxiranyl ring by the amine and transamination of the β-aminovinylketone.

Hydrochloric and hydrobromic acids react readily with aminovinyl ketones I and II at ordinary temperatures with the formation of halogen-substituted 3(2H)-furanones VII-X in yields of 40-56%:



VII, VIII R=H, IX R=Me; VII, IX X=Cl, VIII, X X=Br

The moderate yields of aminofurans III-VI are the result of side reactions, one of which is the opening of the 3(2H)-furan ring by amines. Thus, for example, morpholine reacts readily with the furanone VIII in toluene, probably forming the hydrobromide B which is then rapidly converted in the presence of amine into the oxiranyl-β-morpholinovinyl ketone XII. The retention of the epoxide ring in compound XII in the presence of morpholine is in keeping with the characteristic stability of epoxyketone rings toward amines in nonpolar aprotic solvents [12-14].

The structure of the 3(2H)-furanones III-X was confirmed from IR and PMR spectra. In the IR spectra carbonyl absorption bands were observed in the 1710-1705 cm^{-1} region and conjugated double bonds at 1570-1560 cm^{-1}. In the PMR spectra, two signals were observed from the interacting olefinic protons with a strong negative chemical shift (5.4 ppm for the α-proton and 7.9 ppm for the β-proton); this is characteristic for an enol system, the value J = 2.5 Hz being typical for the 3(2H)-furanone ring [9-11].

EXPERIMENTAL

The progress of the reactions was monitored by TLC using Silufol plates, 2:1 acetone/hexane, and iodine vapor for visualization. IR spectra were run on a Specord-75 IR instrument, and PMR spectra on a Tesla BS-467 (60 MHz) with HMDS as internal standard.

2-Aminomethyl-2-methyl-3(2H)-furanones (III-VI, Table 1). To a solution of 15.5 g (0.1 mole) aminovinyl ketone I in 50 ml isopropanol was added 0.15 mole of the appropriate amine and the mixture kept for 2-3 days (TLC monitoring). The solvent was removed under reduced pressure and the residue fractionated in vacuum. Compounds V and VI were recrystallized from hexane.

2-(1-Haloalkyl)-2-methyl-3(2H)-furanones (VII-X, Table 1). To a solution of 0.1 mole aminovinyl ketone I or II in 10 ml water was added 17.2 ml 36% HCl (0.2 mole) or 25 ml 45% HBr (0.2 mole) and the solution left overnight. The reaction product was extracted with ether, dried over sodium sulfate and, after removing the ether, fractionated under reduced pressures.

(E)-4-Methyl-1,5-dimorpholino-4-hydroxy-1-hexen-3-one (XI). A solution of 1.69 g (0.01 mole) ketone II and 1.3 ml (0.015 mole) morpholine in 10 ml isopropanol was heated at bp for 30 h and the crystals which separated were filtered off. Yield, 42%, mp 165°C. IR spectrum (cm^{-1}): 3370 (OH), 1640 (C=O), 1555 (C=C). PMR spectrum (δ, ppm): 0.85 (3H, d, CH_3), 1.33 (3H, s, CH_3), 2.07-3.77 (18H, m, morpholine protons, CH, OH), 5.30 (1H, d, CH, J = 13 Hz), 7.50 (1H, d, CH, J = 13 Hz). Found, %: C 60.1; H 8.6; N 9.5. $C_{15}H_{26}N_2O_4$. Calculated, %: C 60.4; H 8.8; N 9.4.

4-Methyl-1-morpholino-4,5-epoxy-1-penten-3-one (XII). A solution of 0.95 g (5 mmoles) furanone VIII and 0.9 ml (10 mmoles) morpholine in 5 ml toluene was kept overnight and the precipitated salt filtered off, the solvent removed under reduced pressure and the residue recrystallized from a 1:1 mixture of ethyl acetate and hexane. Yield 53%, mp 127-128°C. IR spectrum (cm^{-1}): 1650 (C=O), 1560 (C=C). PMR spectrum (δ, ppm): 1.39 (3H, s, CH_3), 3.50 (2H, s, CH_2), 3.16-3.80 (8H, m, morpholine protons), 5.21 (1H, d, CH, J = 13 Hz), 7.61 (1H, d, CH, J = 13 Hz). Found, %: C 60.6; H 7.5; N 7.0. $C_{10}H_{15}NO_3$. Calculated, %: C 60.9; H 7.7; N 7.1.

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SYNTHESIS OF 2-SUBSTITUTED TETRAHYDROFURANS

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We have developed a three-stage scheme for the preparative synthesis of 2-substituted tetrahydrofurans from allyl halides and aldehydes to give the first stage – a Grignard reaction – mixed alkoxides, which on treatment with acetic anhydride are converted to 4-acetoxy-1-alkenes. Addition of hydrogen bromide to the latter contrary to Markownikoff's rule gives 4-acetoxy-1-bromoalkanes, which as a result of hydrolysis form 2-R-tetrahydrofurans.

2-Substituted tetrahydrofurans (THF) are important starting materials for the preparation of 2-substituted thiolanes and other five-membered saturated heterocycles. The main methods for the synthesis of compounds of type IIIa-c are based on the use of furfural, which gives secondary alcohols in a Grignard reaction, and these are then dehydrated and hydrogenated [1]. With symmetrical aldehydes or ketones furfural forms furfurylidenealdehydes or ketones, which are reduced and hydrogenated to the required furans [2]. The use of ketones with an asymmetrical structure gives mixtures of isomers. It should be noted in this case that [3-5] are inaccurate concerning the condensation of furfural with methyl alkyl ketones exclusively on the methyl group since a similar reaction of aldehydes occurs mainly on the α-methylene group of the ketone [6]. 2-Phenyl-THF is obtained by reduction of ethyl β-benzoylpropionate followed by dehydration of the 1-phenyl-1,4-butanediol formed [7]. Other synthetic methods, namely, alkylation of THF with olefins in the presence of tert-butyl peroxide [8], acylation of furan followed by reduction and hydrogenation [9], or the use of 3-bromo-1-(1,1-dimethylpropoxy)propane as an initial compound [10] are multistage processes that are complicated to carry out or lead to the formation of mixtures.

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