SYNTHESIS OF 2-FURYLCYCLOPROPANES

NEW MODIFICATION OF THE KISHNER SYNTHESIS OF CYCLOPROPANES

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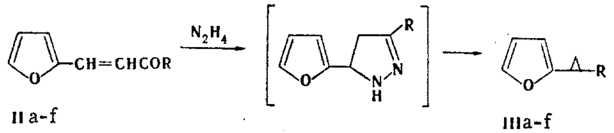
A new one-step modification of the synthesis of cyclopropane-ring-substituted 2-furylcyclopropanes by the Kishner method from α,β-unsaturated ketones of the furan series is proposed. Disubstituted cyclopropanes are obtained in the form of mixtures of the cis and trans isomers, as proved by the PMR and gas–liquid chromatography data.

One of the widely used methods for the preparation of cyclopropanes is decomposition of pyrazolines, usually obtained from α,β-unsaturated ketones, by the Kishner method [1]. This reaction is similar [2] to the well-known method for the reduction of carbonyl compounds by decomposition of hydrazones by the Wolff–Kishner method, for which the modified Huang-Minlon method [3], which makes it possible to obtain hydrocarbons in higher yields without isolation of the hydrazones, is presently widely used.

For the first time we have applied this variant for the synthesis of cyclopropanes from α,β-unsaturated carbonyl compounds. We selected 2-furylcyclopropane derivatives as the subjects of this study. This choice was based on the following circumstances. First, little study has been devoted to furylcyclopropane derivatives, despite the fact that they may be of definite interest for the study of the conjugation of a three-membered ring with an aromatic system. Second, the synthesis of these compounds and especially the parent compound (2-furylcyclopropane) has been fraught with considerable difficulties. Thus, for example, 2-furylcyclopropane was obtained in two steps by the classical method in 25% yield [4]. It was subsequently demonstrated [5] that the 2-furylcyclopropane obtained by this method contains a considerable amount of 2-propenylfuran. It was found that pure 2-furylcyclopropane could be obtained by using 1-(2-furyl)-3-dimethylamino-1-propanone hydrochloride (I) as the starting compound. However, the subsequent decomposition of the intermediate pyrazoline with lithium hydroxide was effective only in the case of less than 4-g samples of the pyrazoline, which made the synthetic operation laborious.

We have found that α,β-unsaturated carbonyl compounds of the furan series (II) are smoothly converted to the corresponding cyclopropanes (IIIa-f) (Table 1) in one step when they are heated with hydrazine hydrate and alkali in the presence of di- or triethylene glycol:



II a-f

IIIa-f

II, IIIa $R=CH_3$; b $R=C_2H_5$; c $R=C_6H_5$; d R = furyl; e R = 5-methylfuryl; f R = cyclopropyl

The yields of furylcyclopropanes (80-85%), which are not restricted by the sample size of the starting ketone and the ease of carrying out the reaction, make it possible to recommend it as a preparative method for the synthesis of compounds of this series. This method has also been found to be applicable for the synthesis of 2-furylcyclopropane (IV) if hydrochloride I is used as the starting compound.

The PMR spectra of III and IV (Table 2) contain signals at strong field at 0.5-1.0 ppm, which are characteristic for the protons of a three-membered ring. However, it should be noted that the signals of the cyclopropane protons may undergo a substantial change in their position as a function of the substituents. Thus when there are two aromatic substituents present, two groups of multiplets – 1-H (0.02-1.4 ppm) and 2-H and 3-H (at weaker field at 1.8-2.4 ppm) – are clearly distinguished in the PMR spectrum. The characteristic absorption of

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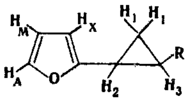
TABLE 1. Physical Constants of the 2-Furylcyclopropanes

Compound	R	bp, °C (mm)	Found, %		Empirical formula	Calc., %		n_D^{20}	d_4^{20}	MR_D		UV (in heptane)		Yield, %
			C	H		C	H			found	calc.	λ_{max}	lg ε	
III[5]	H	127— —128	—	—	C_7H_8O	—	—	1,4791	0,9721	31,51	31,46	223	3,97	50
IIa[1]	CH_3	66 (55)	—	—	$C_8H_{10}O$	—	—	1,4770	0,9492	36,10	36,53	225	3,99	82
IIb	C_2H_5	95 (55)	79,2	8,9	$C_9H_{12}O$	79,4	8,9	1,4802	0,9513	40,43	40,78	224	3,98	80
IIc	C_6H_5	87 (2)	84,7	6,5	$C_{13}H_{12}O$	84,8	6,6	1,5670	1,0902	55,26	55,65	230	4,10	85
IId	Furyl	66 (1)	75,8	5,8	$C_{11}H_{10}O_2$	75,9	5,8	1,5320	1,0935	49,67	49,22	233	4,19	80
IIe[9]	5-Methyl-furyl	81 (2)	—	—	$C_{12}H_{12}O_2$	—	—	1,5305	1,0840	53,63	53,90	236	4,20	80
IIf[8]	Cyclopro-pyl	67 (8)	—	—	$C_{10}H_{12}O$	—	—	1,4972	0,9922	44,91	44,35	224	3,97	81

TABLE 2. Data from the PMR Spectra of



Compound	R	Isomer ratio (cis : trans)	Chemical shifts of the protons, ppm			Chemical shifts of the protons, ppm				SSCC, Hz		
			R group	1-H	2-H	3-H	A=H	M=H	X=H	J_{AM}	J_{AX}	J_{MX}
IV	H		0,6—0,8 (m)[a]	0,6—0,8 (m)	1,5—1,9 (m)	0,6—0,8 (m)	6,93 (q)	6,0 (q)	5,72 (dt)	1,8	0,8	3,0
IIIa	CH_3	3 : 2	0,7—2,01 (m)	—	0,38—2,01 (m)	—	7,07 (q) 7,24 (q)	6,05 (q) 6,18 (q)	5,71 (dt) 5,88 (dt)	1,9 1,7	0,9 0,8	3,2 3,1
IIIf	Cyclopropyl	5,5 : 4,5	0,02—2,15 (m)	—	0,02—2,15 (m)	—	7,10 (q) 7,21 (q)	6,14 (q) 6,18 (q)	5,83 (dt) 5,95 (dt)	1,8 1,8	0,8 0,8	3,1 3,1
IIId	Furyl	3 : 1	—[b]	1,05—1,43 (m)	—	1,93—2,27 (m)	7,03 (q) 6,90 (q)	6,08 (q) 5,95 (q)	5,84 (q) 5,57 (q)	1,9 1,8	0,9 0,7	3,2 3,2
IIIe	5-Methylfuryl	3 : 1	2,01 (s)[c] 5,45—6,1 (m)[d]	1,01—1,38 (m)	—	1,93—2,27 (m)	7,01 (q) 6,95 (q)	6,04 (q) 5,93 (q)	5,45—5,88 (m) 5,45—5,88 (m)	1,9 1,8	0,9 0,9	3,1 3,1
IIIc	C_6H_5		6,7—7,22 (m)	0,86—1,44 (m)	—	1,82—2,40 (m)	6,7—7,22 (m)	6,02 (q)	5,84 (d)	1,8	—[e]	3,1

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[a] When R = H, the signal merges into a single multiplet with the 3-H signal.

[b] The signals of the protons of the R= furyl group coincide with the analogous signals of the other furan ring.

[c] This is the singlet of the protons of the CH_3 group.

[d] The signals of the protons of the 2-methylfuran ring are overlapped by the multiplet from X = H.

[e] The A = H signals are overlapped with the signals of the protons of the phenyl ring.

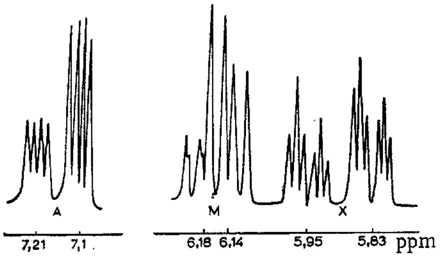

Fig. 1. AMX portion of the PMR spectrum of the protons of the furan ring in IIf.

the protons of a substituted furan ring (AMX system) is observed at 5.5-7.2 ppm. The spin–spin coupling constants (SSCC) of the protons of the furan ring coincide with the literature data [7]: J_{23} = 1.5-2.0, J_{24} = 0.0-1.0, and J_{34} = 3.1-3.8 Hz. We note that the signal of the X portion appears as a doublet of triplets with an additional J constant of 0.8 Hz; this is due to coupling of the allyl type with the methylidyne proton of the cyclopropane ring.

A peculiarity of the spectra of the disubstituted cyclopropanes is doubling of the set of signals from the furan ring protons (Fig. 1). This doubling indicates the presence of a mixture of cis and trans isomers relative to the cyclopropane ring. As seen from Table 2, the AMX portion of the spectrum of the furan protons has similar SSCC for both isomers. All of the disubstituted compounds (except IIIc) had two peaks on their chromatograms; the absence of admixtures of the isomeric (with respect to the cyclopropanes) olefins was demonstrated by means of standards.

Thus the synthesis of 2-furylcyclopropanes by the Kishner method proceeds nonstereospecifically and leads to a mixture of geometrical isomers.[†]

The UV absorption may qualitatively characterize the phenomenon of the so-called conjugation of a three-membered ring with unsaturated groupings. The band of the $\pi-\pi^*$ transition in the spectrum of 2-n-propylfuran has λ_{max} 206 nm (log ε 4.08), as compared with 260 nm (log ε 4.23) in the spectrum of 2-(2-propenyl)furan. As seen from Table 1, a bathochromic shift as compared with 2-n-propylfuran is also observed for all of the 2-furylcyclopropane derivatives. The introduction of a methyl substituent in the cyclopropane ring changes the position of λ_{max} only slightly. It is interesting that the introduction of a second cyclopropane ring also does not substantially affect the position of λ_{max}. On passing to cyclopropane derivatives with two aromatic substituents the band undergoes a bathochromic shift of 7-13 nm as compared with the monosubstituted compounds, and a corresponding increase in log ε is observed. These data can be interpreted as a manifestation of conjugation of the three-membered ring with the aromatic substituents.

Several absorption bands of stretching vibrations of the C–H bonds of furan and cyclopropane rings at 3000-3150 cm^{-1} are observed in the IR spectra of all of the 2-furylcyclopropane derivatives obtained. In addition, they contain a strong absorption band at 1017-1025 cm^{-1}, which is characteristic for cyclopropane derivatives [6]. The absorption bands at 1600 and 1520 cm^{-1} can be assigned to the absorption of the furan ring.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were obtained with a Varian C-60-H spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of thin layers of the compounds were recorded with an IKS-22 spectrometer. The UV spectra of heptane solutions of the compounds were recorded with an SF-4 spectrophotometer. Analysis of the products by gas–liquid chromatography (GLC) was carried out with an LKhM-8MD chromatograph with a 200- by 0.4-cm column filled with PEG 6000 (10%) on Chromosorb W or FS (15%) on Chromosorb G with helium as the carrier gas.

Disubstituted Furylcyclopropanes (IIIa-f). A 0.75-mole sample of hydrazine hydrate was added with shaking to a mixture of 0.25 mole of the appropriate furfurylidene ketone IIa-f and 200 ml of diethylene glycol, after which the mixture was allowed to stand for 1 h. It was then treated with 0.25 mole of granulated KOH, and the mixture was refluxed for 1 h. The reflux condenser was then replaced by a condenser for distillation, and heating was continued on an oil bath at 230-260° until nitrogen evolution ceased (~2.5 h). The water and excess hydrazine hydrate were removed during the distillation procedure. The reaction mixture was cooled and diluted with water, and the aqueous layer was extracted several times with ether. The ether extracts were

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[†] We note that cyclopropanes IIIa,e,f have been previously regarded [8, 9] as individual compounds without allowance for cis–trans isomerism.

washed successively with water, 20% HCl, and water and dried successively with K_2CO_3 and sodium metal. The ether was removed by distillation, and the product was vacuum distilled. In the preparation of low-boiling 2-furylcyclopropane derivatives the latter were removed together with the water and excess hydrazine hydrate by distillation and were then extracted from the distillate by means of ether and obtained from the extracts as in the method described above.

2-Furylcyclopropane (IV). A 42-g (0.2 mole) sample of 1-(2-furyl)-3-dimethylamino-1-propanone was added with shaking to a mixture of 150 ml of diethylene glycol, 11.2 g (0.2 mole) of KOH, and 33 ml (0.6 mole) of hydrazine hydrate, after which periodic shaking was continued for another 30-40 min. The mixture was then heated on an oil bath at 140° for 4 h, after which it was allowed to stand for 1 h without heating. Another 11.2 g of KOH was added, and the mixture was heated to 230° (bath temperature) after the condenser was adjusted for distillation, during which nitrogen was evolved, and the 2-furylcyclopropane distilled from the mixture along with the water and excess hydrazine hydrate. The organic layer was separated from the aqueous layer and washed successively with water, rapidly with 2.5% HCl and 20% KOH, and water, after which it was dried successively with K_2CO_3 and sodium metal. Distillation over Na in a stream of nitrogen gave 11.2 g (50%) of 2-furylcyclopropane.

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SYNTHESIS OF 2-PHENYL-4-HYDROXYBENZOFURAN DERIVATIVES

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2-Phenyl-4-hydroxybenzofuran was obtained by dehydrogenation of 2-phenyl-4-oxo-4,5,6,7-tetrahydrobenzofuran under the influence of sulfur. The transformations of 2-phenyl-4-hydroxybenzofuran and its derivatives were studied.

In contrast to 5- and 6-hydroxybenzofuran derivatives, 4-hydroxybenzofuran derivatives are relatively inaccessible and have not been studied in detail. However, they are of particular interest as heteroanalogs of biologically active 4-hydroxyindole derivatives [1].

The present research is a continuation of our studies of 4-hydroxybenzofuran derivatives [2]. We found that 2-phenyl-4-hydroxybenzofuran (Ia) is formed in high yield in the dehydrogenation of 2-phenyl-4-oxo-4,5,6,7-tetrahydrobenzofuran [3] with sulfur. Compound Ia was previously isolated in very low yield in the reaction of resorcinol and ω-diazoacetophenone [4].

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