INDOLES

XXXIV.* O-PHENYLHYDROXYLAMINE AS THE O-ANALOG OF PHENYLHYDRAZINE IN THE FISCHER REACTION

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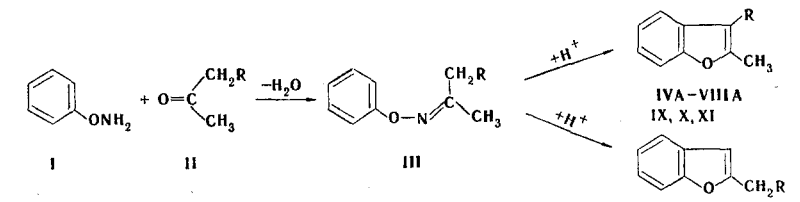
Under the conditions of the Fischer reaction, O-phenylhydroxylamine forms mixtures of isomeric (with respect to substitution in the 2 and 3 positions) benzofurans with methyl ketones. Only 3-substituted 2-methylbenzofurans were isolated when methyl ketones with a "strongly activated" methylene group were used as the carbonyl component.

In an attempt to use O-phenylhydroxylamine (I) as the O-analog of phenylhydrazine in the synthesis of tryptamine [2], we encountered an unusual course of the Fischer reaction, even for the simplest ketones; this was also the subject of study in the present paper.

The cyclization of phenylhydrazones of unbranched methyl ketones under the usual conditions gives only 3-substituted 2-methylindoles [3]. However, it was recently shown that mixtures of isomeric indoles are formed in very strongly acid media ($H_0 > -4.6$), i.e., cyclization is realized at the α-CH_2 and α-CH_3 groups [4].

There are a limited number of studies [5-10] pertaining to the use of I in the Fischer reaction, and the O-phenyl ether of the oxime of an unsymmetrical ketone (2-butanone) was cyclized only in one of them [9]; in this case, it was qualitatively noted that the reaction proceeded ambiguously.

We have investigated the cyclization of I with ketones of the CH_3COCH_2R type (IIa-e); a) $R = CH_3$; b) $R = C_2H_5$; c) $R = C_6H_5$; d) $R = CH_2C_6H_5$; e) $R = CH_2CH_2OH$. On the basis of the UV, IR, and PMR spectra and the results of gas-liquid chromatography (GLC) of the compounds obtained, it was established that a mixture of two isomeric (A and B) benzofurans (IV-VIII) is formed as a result of the reaction, while in the case of the analogous reaction of I with carbonyl compounds with a "strongly activated" methylene group (IIf, g) (f $R = COOC_2H_5$; g $R = COCH_3$) or $CH_3C(=NH)CH_2CN$ (IIh), only 3-substituted 2-methylbenzofurans A (IX-XI) are formed.



I II III

IV $R=CH_3$; V $R=C_2H_5$; VI $R=C_6H_5$; VII $R=CH_2C_6H_5$;
VIII $R=CH_2CH_2OH$; IX $R=COOC_2H_5$; X $R=COCH_3$; XI $R=CONH_2$

The reaction of the hydrochloride of I with the hydrochloride of diacetonitrile (IIh) yielded 2-methylbenzofuran-3-carbamide (XI), which is apparently formed as a result of partial hydrolysis of nitrile XII.

*See [1] for communication XXXIII.

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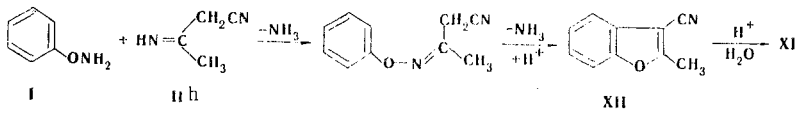
TABLE 1. Physical Constants and Analysis of the Synthesized Benzofurans (IV-XI)

Benzofuran	R	mp, °C	bp, °C (mm)	R_f*	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, %
IV	CH_3		89—90 (10)	0,86	$C_{10}H_{10}O$	80,8	7,0	81,6	6,9	65
V	C_2H_5		110—112 (16)	0,85	$C_{11}H_{12}O$	81,9	7,7	82,4	7,6	70
VI	C_6H_5		125—127 (1)	0,80	$C_{15}H_{12}O$	85,3	5,7	86,0	5,8	52
VII	$CH_2C_6H_5$		143—145 (1)	0,78	$C_{16}H_{14}O$	85,9	6,5	86,4	6,4	61
VIII	CH_2CH_2OH		128—130 (2)	0,86†	$C_{11}H_{12}O_2$	74,4	7,1	75,0	6,9	68
IX	$COOC_2H_5$	35—37	108—110 (2)	0,84‡	$C_{12}H_{12}O_3$	70,0	5,8	70,6	5,9	79
X	$COCH_3$	28—30	98—100 (1)	0,75‡	$C_{11}H_{10}O_2$	75,0	6,1	75,9	5,8	48
XI	$CONH_2$	173—175		0,26	$C_{10}H_9NO_2$	68,7	5,3	68,6	5,2	48

*Chromatography in a thin layer of activity II Al_2O_3 [chloroform-benzene (1:1)] and development with iodine.

† Benzene–isopropyl alcohol (9:1).

‡ Benzene–isopropyl alcohol (14:1).

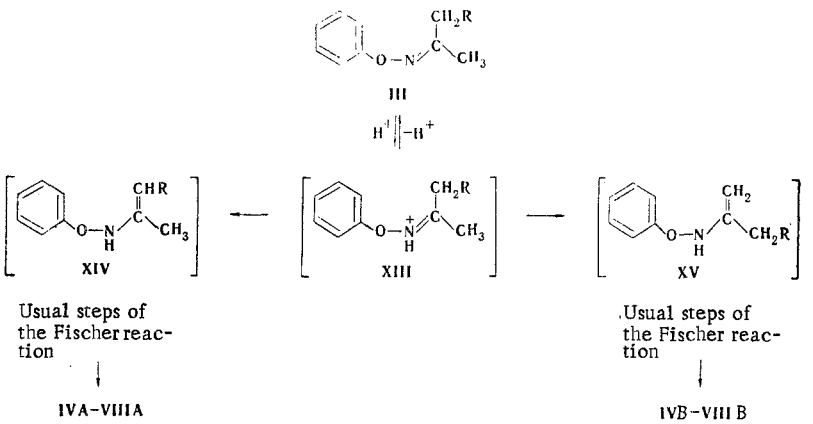


I IIh XII

Benzofurans IV-XI (Table 1) were obtained by heating I and IIa-h in isopropyl alcohol with an equimolar amount of hydrochloric acid.

The structures and compositions of the mixtures of IV-XI were determined from the UV, IR, and PMR spectra and GLC data. The UV spectra (Table 2) have three absorption bands characteristic for benzofuran at 247, 275, and 282 nm. The absorption bands of benzofuran [11] are present in the IR spectra (Table 3). The PMR spectra of IV-VIII have signals that are affiliated with isomers A and B, while the PMR spectra of IX-XI correspond only to isomer A (Table 4). The ratio of isomers A and B was determined by integration of the PMR spectra of IV-VIII. The signal of the 3-H proton of isomer B, which is found at 6.20 ± 0.05 ppm, and the singlet at 2.32 ppm of isomer A, which corresponds to the methyl group in the 2 position, were used for the calculations. The shift of this singlet to weak field for VI and IX-XI is due to the magnetic anisotropy of the benzene ring and the C=O double bond in the 3 position. The ratio of reaction products found was confirmed by analysis of the mixtures of isomers by means of GLC (Tables 5 and 6).

Since there is no basis for doubting that the production of benzofurans from I is a process similar to the Fischer synthesis of indoles, we will examine the mechanism of this reaction from the point of view of the general concept of this synthesis.

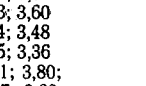


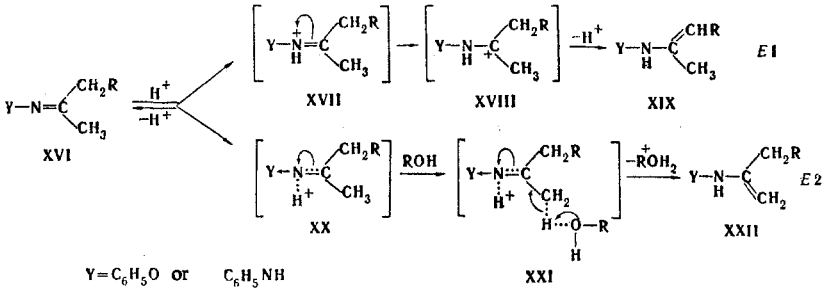
It is well known [1, 12] that the slowest step of the Fischer reaction is tautomerization of the hydrazone molecule (in our case, oxime ether III). The formation of two isomeric benzofurans (A and B) as a result of the reaction is apparently associated with two possible directions of "migration" of the double bond in the III molecule, which are due to the different mechanisms; as we see it, these mechanisms are similar to the E1 and E2 elimination mechanisms.

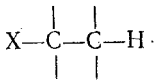
TABLE 2. UV spectra of Benzofurans IV-XI

Benzofuran	λ_{max}, nm	lg ε
IV	247; 275; 282	4,02; 3,46; 3,40
V	247; 276; 282	3,94; 3,40; 3,36
VI	251; 275; 283	4,04; 3,73; 3,60
VII	247; 276; 283	4,11; 3,54; 3,48
VIII	246; 275; 281	4,10; 3,45; 3,36
IX	216; 220; 245; 255; 274; 282; 310	4,11; 4,11; 3,80; 3,81; 3,67; 3,62; 3,03
X	228; 256; 271	4,18; 3,94; 4,04
XI	213; 233; 261; 294; 306	4,18; 4,00; 4,06; 4,01; 3,98

Let us consider the fragment responsible for the direction of the β-elimination reaction, which leads to the formation of structures XIV and XV.

The double bond that is ruptured during protonation  plays the role of the split-off group during β-elimination in the cases under examination, and the lower the basicity of the nitrogen, the more hindered is its protonation; this in turn complicates cleavage of the N=C bond.



In the usual cleavage reactions, this is analogous to hindrance of detachment of substituent X from the  grouping, which usually leads to predominance of the E2 mechanism [13].

In the case of the normal Fischer reaction ($Y = C_6H_5NH$), the formation of an enehydrazine occurs via an E1 mechanism. Structure XVIII, which is stabilized by splitting out of a proton with transfer to the thermodynamically more favorable structure XIX with a maximum number of branches attached to the double bond, is formed after protonation of the β−N atom (XVII). In this case, there is practically no participation of the solvent in the splitting out of the proton.

In strongly acid media [4], due to the formation of a diprotonated structure ($Y = C_6H_5\overset{+}{N}H_2$), a portion of the basic fragment becomes such a strong acceptor (−I) that the hydrogen atoms in the α-positions be-

TABLE 3. Principal Bands (cm^{-1}) in the IR Spectra of Benzofurans IV-XI*

IV	V	VI	VII	VIII	IX	X	XI	Possible assigment
				3200–3500			3380	ν_{OH}, ν_{NH}
3070	3060	3060	3060	3070	3060	3060	3080	ν_{CH} aromatic
2840–3000	2840–3000	2840–3000	2840–3000	2840–3000	2840–3000	2840–3000	2840–3000	ν_{CH_3}, ν_{CH_2}
					1710	1675	1695	$\nu_{C=O}$
1600, 1500	1605, 1490	1600, 1500	1605, 1495	1605, 1590	1600, 1450	1580, 1450	1595, 1500	ν (aromatic ring)
1460	1450	1460	1455	1455	1450		1455	
1475, 1380	1470, 1385	1470, 1390	1470, 1385	1480	1480, 1385	1480, 1385	1375	δ_{CH_3}, δ_{CH_2}
1260	1250	1255	1250	1255	1240	1250	1240	ν_{C-O}
755	750		765	750			760	Four adjacent protons

*The spectra of IV, IX, and X were recorded with a Jasco IR-S spectrometer, while those of V-VIII and XI were recorded with a UR-20 spectrometer, from thin layers (IV, V, VII, and VIII), from chloroform solutions (VI, IX, and X), and from a KBr pellet (XI).

TABLE 4. PMR Spectra of Benzofurans IV-XI*

Benzofurans	R	Isomer A			Isomer B				Aromatic protons of A and B, δ, ppm
		2-CH_3	3-R		2-CH_2		R	3-H	
		δ, ppm	δ, ppm	J, Hz	δ, ppm	J, Hz	δ, ppm	δ, ppm	
IV	CH_3	2,32 s	2,09 s		2,77 q	7,5	1,30 t	6,23 s	6,95—7,45 m
V	C_2H_5	2,32 s	CH_3 0,98 t	7,5	2,70 q	7,5	CH_3 1,22 t	6,20 s	7,00—7,50 m
			CH_2 2,62 q	7,5			CH_2 1,75 sex	7,5	
VI	C_6H_5	2,41 s	6,65—7,55 m		3,94 s		6,65—7,55 m	6,15 s	6,65—7,55 m
VII	$CH_2C_6H_5$	2,30 s	CH_2 3,85 s		2,92 s		CH_2 2,92 s	6,16 s	6,65—7,40 m
			Ar 6,65—7,40 m				Ar 6,65—7,40 m		
VIII	C_2H_4OH	2,32 s	CH_2 2,73 t	6,0	2,78 t	7,5	CH_2 1,88 q	6,0	6,20 s	6,95—7,40 m
			OH 3,25 s				OH 3,25 s		
			CH_2 3,56 t	6,0			CH_2 3,67 t	6,0	7,05—8,05 m
IX	$COOC_2H_5$	2,71 s	CH_3 1,42 t	6,8					
			CH_2 4,35 q	6,8					7,00—7,50 m
X	$COCH_3$	2,70 s	2,50 s						
XI	$CONH_2$	2,52 s							6,95—7,50 m

*Abbreviations: s is singlet, t is triplet, q is quartet, sex is sextet, and m is multiplet.

TABLE 5. Gas-Liquid Chromatographic Analysis of Benzofurans IV-X

Benzofuran	Relative retention time*			
	column 1†		column 2‡	
	A	B	A	B
IV	0,10	0,09	0,78	0,71
V	0,11	0,11	1,07	1,07
VI	1,38	1,87	7,14	7,85
VII	1,98	2,39	8,92	11,71
VIII	1,66	2,13	3,07	3,57
IX	0,53		3,21	
X	0,57		2,28	

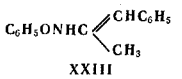
*Determined relative to indole.
† Column 1 was 10% polyethylene glycol 3000 on Porolite containing 1% KOH.
‡ Column 2 was 5% SE-30 on Chezasorb.

TABLE 6. Ratio of Isomers A and B in Mixtures of Benzofurans IV-VIII

Benzofuran	R	A/B ratio	
		PMR	gas-liquid chromatography
IV	CH_3	0,82	0,78
V	C_2H_5	0,54	—
VI	C_6H_5	1,46	1,62
VII	$CH_2C_6H_5$	0,61	0,59
VIII	C_2H_4OH	0,43	0,39

come considerably more acidic. In this case, the hydrogen, under the influence of the nucleophiles present in the reaction medium, will be split out via a synchronous mechanism (E2) from the most "acidic" group (CH_3) to form enehydrazine XXII.

If Y is a sufficiently strong acceptor [in our case Y = C_6H_5O with a −I effect, the presence of which is proved by a comparison of the pK_a values (4.84 for phenylhydrazine, 2.10 for I)], that acceptor effect favors the possibility of the occurrence of the process via an E2 mechanism, even in weakly acidic media. The electronic and steric factors due to substituent R should, of course, affect the mechanism of the formation of the olefinic bond. It is apparent from the data in Table 6 that if R is alkyl, isomer B predominates (E2). This is associated with the higher acidity of the protons of the CH_3 group as compared with the protons of the CH_2 group because of the +I effect of the alkyl groups. The fraction of isomer A increases on passing from R = CH_3 to R = C_6H_5. This reaction trend is explained by the possibility of the formation of thermodynamically more favorable product XXIII, in which conjugation of the resulting double bond with the benzene ring of the substitutent and intensification of the acidity of the CH_2 group due to the acceptor effect of the phenyl radical are possible.



XXIII

When the substituent is a strong electron-acceptor group (R = $COOC_2H_5$, $COCH_3$, CN), only isomer A is formed (Table 1), since the formation of thermodynamically favorable intermediate XIV is also kinetically favorable.

EXPERIMENTAL

The IR spectra of liquid films, CCl_4 and $CHCl_3$ solutions, and KBr pellets of the compounds were recorded with Jasco IR-S (NaCl prism) and UR-20 spectrometers. The UV spectra of ethanol solutions were recorded with a Hitachi EPS-3T spectrometer. The PMR spectra of CCl_4 solutions were recorded with a JNM-4H-60 spectrometer with hexamethyldisiloxane as the internal standard. The GLC analysis was performed with a Yanaco G-800 chromatograph with two 2-m-long columns with a diameter of 4 mm: the first column contained polyethylene glycol 3000 on Porolite with 1% KOH, the second column contained 5% SE-30 on Chezasorb. The column temperature was 170°, and the carrier gas (H_2) flow rates were 75 and 100 ml/min, respectively. The detector was a catharometer.

O-Phenylhydroxylamine (I). This compound was obtained in 15% yield via the method in [14], except that the reaction was carried out in benzene rather than in methylcyclohexane. The product had bp 80° (10 mm), n_D^{20} 1.5550, and pK_a 2.10 (determined by titration with 0.1 N hydrochloric acid with a Janagimoto automatic titrator in 80% Methyl Cellosolve). IR spectrum (liquid film): 3250 cm^{-1} (ν_{NH_4}). UV spectrum (ethanol), λ, nm (log ε): 220 (3.98), 270 (3.23), 277 (3.18).

Method for the Synthesis of Benzofurans IV-XI. A 50-ml sample of isopropyl alcohol containing 5.2 ml of concentrated hydrochloric acid was added to a solution of 5.4 g (0.05 mole) of O-phenylhydroxylamine and 0.05 mole of ketone IIa-g in 50 ml of isopropyl alcohol, and the solution was refluxed for 5 h. The alcohol was then removed on a rotary evaporator, and the residue was treated with water. The resulting oil was extracted with three 30-ml portions of benzene. The combined benzene extracts were dried with magnesium sulfate, the benzene was removed by distillation, and the residue was vacuum distilled in a stream of nitrogen. The physical constants and yields of the synthesized compounds are presented in Table 1.

A double amount of hydrochloric acid was used in the case of the reaction with diacetonitrile (IIh).

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