REACTIONS OF SCHIFF BASES WITH ALKYL VINYL ETHERS*

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We have previously reported a diene condensation of a new type, consisting in the reaction of Schiff bases with alkyl vinyl ethers [1]. Before this communication there was no information in the literature concerning the possibility of such a reaction. Later, in a series of investigations we showed that various unsaturated ethers such as dihydropyran, dihydro-2-methylfuran [2], ethyl ethynyl ether [3], and also their analogs—ketene and vinyl sulfides [3, 4]—react with Schiff bases. It was shown that the reactions of Schiff bases with unsaturated ethers in presence of Lewis acids (BF_3, $AlCl_3$, $AlBr_3$) are special cases of the more general reaction of imines with unsaturated ethers, which occurs in an acetic acid medium [5].

In the present paper we give a more detailed account of the results reported in a letter to the Editor [1] and also describe some new examples of the reactions of alkyl vinyl ethers with Schiff bases. The adducts obtained are listed in Table 1. It has been found [3] that in absence of catalyst the reaction of Schiff bases with alkyl vinyl ethers does not go. On addition of a catalyst (fractions of one percent) even at room temperature reaction starts slowly and is complete after 1-2 h. As catalyst we used BF_3 preferentially. Reactions were conducted in solvents such as ether, benzene, and ethyl acetate, taken in an amount sufficient for the dissolution of the Schiff base. The isolation of the reaction products was usually effected by vacuum fractionation, but—in the case of crystalline adducts—sometimes by crystallization from the reaction mixture. As a result of the reaction 4-alkoxy-2-aryl-1,2,3,4-tetrahydroquinoline derivatives (I) were usually formed. These compounds are fairly stable under the usual conditions, but in the course of the reaction or in the distillation elimination of the alkoxy group tends to occur to some extent with formation of the corresponding 1,2-dihydroquinolines (II). As is well known [6], the latter readily polymerize. This may explain the formation of a considerable polymeric residue in a number of cases. By heating the compounds (I) with p-toluenesulfonic acid or by the action of oxidizing agents we may readily convert them into the corresponding quinolines (IV). It is probable that in the first case the elimination of an alcohol with formation of the 1,2-dihydroquinoline (II) may occur initially; this is then dehydrogenated, and here part of the 1,2-dihydroquinoline molecules must act as hydrogen acceptor. In this case polymer formation is observed, which, as stated above, is related to the instability of 1,2-dihydroquinolines. As a result, the yields of quinolines obtained by the action of p-toluenesulfonic acid do not exceed 50%. In the action of an oxidizing agent, such as $KMnO_4$ in acetone at room temperature, the hydrogen in the 1,2-positions is probably oxidized initially with formation of 4-alkoxy-3,4-dihydroquinolines (III), after which the elimination of the alcohol goes readily. In this case the yields of quinolines are more than 90%. These reactions can be represented by the scheme on p. 1231.

It is interesting that in the reaction of ethyl vinyl ether with N-benzylidene-2-naphthylamine the primary adduct—1-ethoxy-1,2,3,4-tetrahydro-3-phenylbenzo[f]quinoline—was not isolated at all: 3-phenylbenzo[f]quinoline (XV) immediately began to crystallize from the reaction mixture. In the reaction of ethyl vinyl ether with N-benzylidene-1-naphthylamine a mixture of 4-ethoxy-1,2,3,4-tetrahydro-2-phenylbenzo[h]quinoline (XVI) and 2-phenylbenzo[h]quinoline (XVIa) was formed. The primary adduct formed by N-benzylideneaniline with ethyl isopropenyl ether was also very unstable because of the linkage of the ethoxy group to a tertiary carbon atom. As a result, the yield of adduct was low, though the reaction went very vigorously. On the other hand, the adduct formed with ethyl propenyl ether was stable. The character of the alkoxy group has little effect on the reaction: reaction went just as

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TABLE 1. Adducts Formed by Schiff Bases with Vinyl Ethers

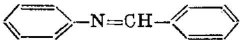
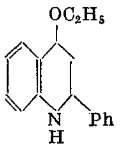
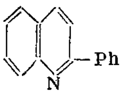
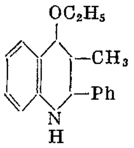
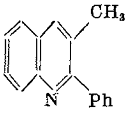
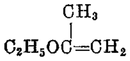
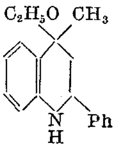
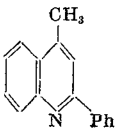
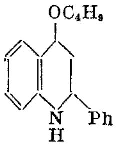
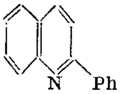
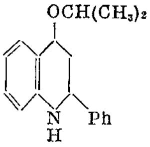
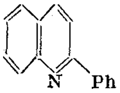
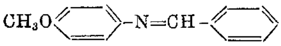
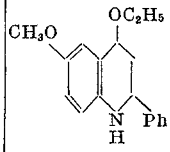
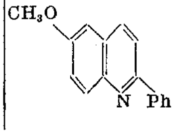
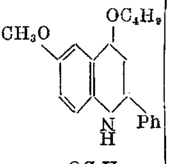
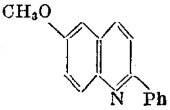
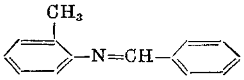
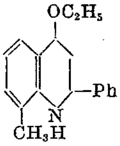
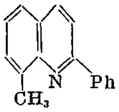
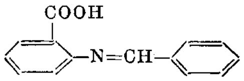
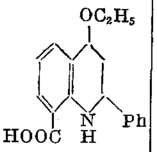
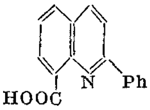
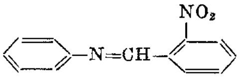
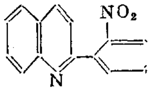
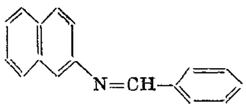
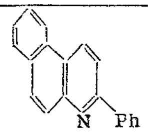
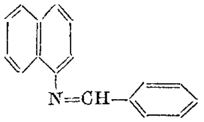
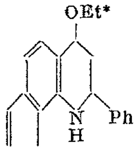
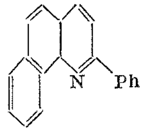
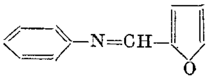
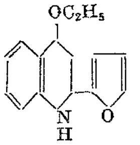
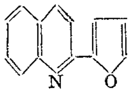
Schiff base	Vinyl ether	No.	Tetrahydro-quinoline	No.	Quinoline
	$C_2H_5OCH=CH_2$	V		Va	
Ditto	$C_2H_5OCH=CHCH_3$	VI		VIa	
»	 $C_2H_5O\overset{CH_3}{\overset{\vert}{C}}=CH_2$	VII		VIIa	
»	$C_4H_9OCH=CH_2$	VIII		Va	
»	$(CH_3)_2CHOCH=CH_2$	IX			—
»	$ClCH_2CH_2OCH=CH_2$		—	Va	
	$C_2H_5OCH=CH_2$	X		Xa	
Ditto	$C_4H_9OCH=CH_2$	XI		Xa	
	$C_2H_5OCH=CH_2$	XII		XIIa	
	$C_2H_5OCH=CH_2$	XIII		XIIIa	
	Ditto	—	—	XIV	

TABLE 1 (Continued)

Schiff base	Vinyl ether	No.	Tetrahydro-quinoline	No.	Quinoline
	$C_2H_5OCH = CH_2$	—	—	XV	
	»	XVI		XVIa	
	$C_2H_5OCH{=}CH_2$	XVII		XVIIa	

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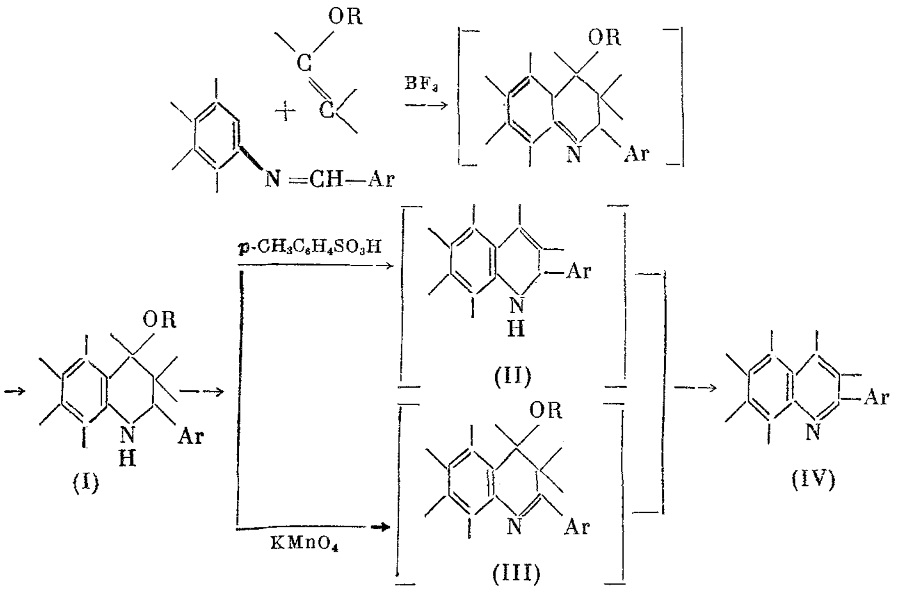
* In admixture with (XVIa).

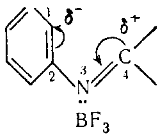


smoothly with isopropyl and butyl vinyl ethers as with ethyl vinyl ether. The low yields of adducts obtained with these ethers in some cases are explained by the difficulty in the isolation of high-boiling adducts.

2-Chloroethyl vinyl ether also reacts with N-benzylideneaniline, but in the fractionation of the reaction product the 2-chloroethoxy group is eliminated completely from the primary adduct. As a result only 2-phenylquinoline containing some 1,2-dihydro-2-phenylquinoline was isolated. On the other hand, phenyl vinyl ether was found to be inactive and did not give an adduct with N-benzylideneaniline under similar conditions. As regards the effect of substituents in the anils on the reaction it was found that all the substituted anils tried reacted equally readily with alkyl vinyl ethers. The differences in the yields must rather be attributed to the low stability of the primary adducts, leading to the formation of polymers in the course of the reaction and making isolation difficult.

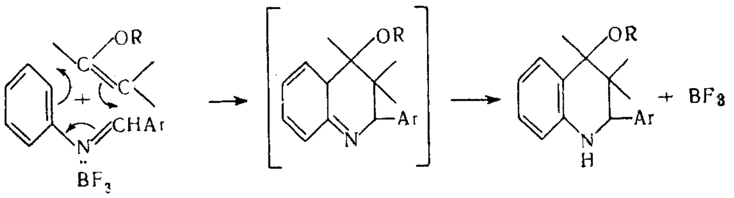
4-Alkoxy-2-aryl-1,2,3,4-tetrahydroquinolines (I) have very feeble basic properties. They do not give picrates and they do not dissolve in dilute mineral acids. For a number of tetrahydroquinoline derivatives (V, VIII, IX, XI, XIII, XVII) we determine the infrared spectrum, which contained absorption bands of the NH bond at 3400-3415 cm^{-1}. In the case of N-benzylideneaniline and N-furfurylideneaniline crystalline adducts with ethyl vinyl ether was obtained, and it was shown that of the possible isomers containing a partially hydrogenated pyridine ring only one was formed, or, in view of the difficulty of isolating these adducts, we may say mainly one isomer. This fact is very important for the discussion of the mechanism of the reaction.

The mechanism of diene condensations has been the subject of extensive controversy. It has now become clear that the numerous diene condensations which are unified by a common scheme of addition of the dienophile to the diene system in the 1,4-position, cannot be attributed to the operation of any single reaction mechanism, either from the point of view of the order of the addition of the reactants (one- or two-stage) or from the point of view of the type of electron transfer (homolytic or heterolytic) [7-12]. An important factor in diene condensations, whose significance has often not been taken into account, is the relative electronic properties of the diene system and the double bond of the dienophile. In most classical diene condensations the diene is an electron donor, whereas the dienophile acts as an electron acceptor. It was shown recently [13] that diene condensations exist in which the electronic properties of the components are reversed. For example, in hexachlorocyclopentadiene the electronegative chlorine atoms withdraw the π-electrons of the diene system and thereby give it electron-acceptor properties. This shows itself in a greater ease of reaction between hexachlorocyclopentadiene and electron-donor dienophiles and in more difficulty in reactions with electron-acceptor dienophiles. From this point of view the behavior of alkyl vinyl ethers toward Schiff bases becomes understandable. As is well known, alkyl vinyl ethers have enhanced nucleophilic power. The diene system of Schiff bases, which contains a nitrogen atom, also has nucleophilic properties. It is natural, therefore, that alkyl vinyl ethers do not react with free Schiff bases. On the other hand, there are data which show that the C=C−N=C diene systems in oxazoles are able to react with such electron-acceptor dienophiles as maleic anhydride [14]. In presence of acidic agents Schiff bases form iminium salts. Thus, we have previously isolated the complex formed by N-benzylideneaniline with boron trifluoride [3]. It may be supposed that in this complex strong polarization of the double bonds occurs:



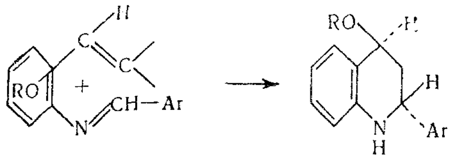
The diene system as a whole, and also the carbon atom in the 4-position, acquires electron-acceptor properties which are probably more marked than in any previously known diene system. This may explain the high reactivity shown by alkyl vinyl ethers in this case and the passivity of dienophiles with electron-acceptor substituents. In the latter the double bond has electron-acceptor properties, and although such dienophiles as acrolein, methyl acrylate, and vinyl halides are active toward many dienes, they do not react with Schiff bases under similar conditions. However, the role of the catalyst does not consist exclusively in the conferment of electron-acceptor properties on the diene system of the Schiff base. According to the literature [15, 16], in Schiff bases the amine ring, as a result of the competing interaction of the π-electrons of the azomethine link and the unshared electron pair of the nitrogen atom with its unsaturated system, is turned at an angle of about 60° relative to the plane of the remaining part of the molecule. On quaternization, the unshared electron pair of the nitrogen is blocked, and the molecule, and therefore the diene system, acquires a planar configuration.

An essential factor is that the tetrahydroquinoline derivatives formed in the reaction of Schiff bases with alkyl vinyl ethers have extremely weak basic properties, which makes the transfer of the catalyst from the product to a new Schiff base molecule possible. In view of the polarity of the reactants and the fact that the reaction is catalyzed by acidic agents, and also the known tendency for alkyl vinyl ethers to react by an ionic mechanism, it may be considered that the reaction is a heterolytic one. This is confirmed by the unequivocal structural orientation in the reaction, corresponding to the polarity of the reactants. In accordance with modern views [10, 17] we may suppose that in the transition state the diene system and the dienophile in coming together form a six-membered ring, in which the synchronous transfer of three electron pairs then occurs:

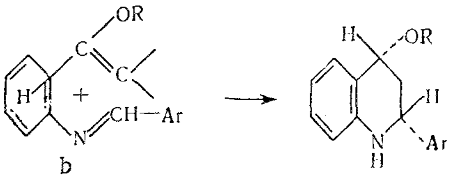


Structural orientation in the reaction was proved by conversion of the ethyl propenyl and ethyl isopropenyl ether adducts into 3- and 4-methyl-2-phenylquinolines respectively. If the principle of the cis addition of reagents is preserved, in the case of unsubstituted alkyl vinyl ethers we may expect the formation of two isomers with cis and trans disposition of the alkoxy and aryl groups. The isolation of only one isomer in the reactions of ethyl vinyl ether with N-benzylideneaniline and N-furfurylideneaniline indicates the stereospecificity of the reaction, which may explain the predominant formation of the endo or exo orientation of the transition state. It is known [8, 12] that in classical diene synthesis the predominant endo orientation of the components is explained by the principle of accumulation of unsaturation or the principle of the accumulation of unshared electron pairs. If it is assumed that in the reactions of alkyl vinyl ethers with Schiff bases endo orientation (a) of the reacting components also occurs, it must be considered that the 1,2,3,4-tetrahydroquinoline derivatives (I) formed are trans, and not cis, isomers; cis isomers would be formed with exo orientation (b) of the components.

It is known that the formation of an endo-orientated complex, which is thermodynamically less stable than an exo-oriented complex, is favored by low temperature. In the present case the reactions were conducted at temperatures which did not usually exceed 35-40°. The use of high reaction temperatures was prevented by the low stability of the adducts formed.



a



b

EXPERIMENTAL

4-Ethoxy-1,2,3,4-tetrahydro-2-phenylquinoline (V). To 91 g of N-benzylideneaniline dissolved in 250 ml of dry ether we added 1 g of BF_3 etherate and then 36 g of ethyl vinyl ether. The temperature of the reaction mixture then rose from 22 to 38°. After the temperature had fallen again to the temperature of the room (about 3 h), the mixture was washed with 10% NaOH solution and water and was dried over $MgSO_4$. On vacuum fractionation we recovered 36 g of N-benzylideneaniline and isolated a fraction of b. p. 158-159° (1.5 mm), which crystallized on standing. After recrystallization from hexane we obtained 48 g of (V) (63.3% yield on the amount of N-benzylideneaniline that reacted).

Under analogous conditions we obtained the adducts (VI)-(XIII) and (XVII), the properties of which are given in Table 2. The reaction of N-benzylideneaniline with ethyl vinyl ether in presence of $AlCl_3$ or $AlBr_3$ went in the same way as with BF_3 etherate with formation of (V).

2-Phenylquinoline (Va). A mixture of 4.5 g of (V) and 0.01 g of p-toluenesulfonic acid was heated in a vacuum at about 100°. The alcohol liberated was condensed in a trap cooled with solid carbon dioxide. When no more alcohol was liberated, the residue was vacuum-fractionated. We obtained a fraction of b. p. 140-142° (2 mm), which crystallized. After recrystallization from hexane we obtained 1.8 g (50%) of (Va). By the same method we prepared the quinolines (VIa), (VIIa), (Xa), and (XVIIa), whose properties are given in Table 3.

3 g of (V) was dissolved in 50 ml of dry acetone, and a solution of 3 g of $KMnO_4$ in acetone was added. The mixture was left overnight, after which the precipitate of MnO_2 was filtered off, acetone was distilled off, and the residue was extracted with benzene. Benzene was driven off, and we obtained 2.2 g of (Va) (90.5% yield). In a similar way we prepared the quinolines (Xa) and (XIIIa) (see Table 3).

Reaction of N-Benzylideneaniline with 2-Chloroethyl Vinyl Ether. 0.3 g of BF_3 etherate was added to a solution of 9 g of N-benzylideneaniline in 75 ml of ether, and 5 g of 2-chloroethyl vinyl ether was then added dropwise at 22°. The temperature of the reaction mixture rose to 25°. The mixture was left overnight and then washed with

TABLE 2. Characteristics of Tetrahydroquinolines Isolated

Cpd No.	B. p., °C (p, mm)	M. p., °C	n_D^{20}	Found, %		Molecular formula	Calculated, %		Yield, %
				C	H		C	H	
V	158—159 (1,5)	72—73 (From hexane)	1,5950	80,49 80,56	7,41 7,52	$C_{17}H_{19}NO$	80,59	7,56	63,3*
VI	164—165 (1,5)	—	1,5920	80,51 80,59	8,05 8,12	$C_{18}H_{21}NO$	80,86	7,92	69
VII	165—170 (1,5)	105—106 (From hexane)	—	80,28 80,28	7,97 7,73	$C_{18}H_{21}NO$	80,86	7,92	12
VIII	170—171 (1)	—	1,5705	80,88 80,79	8,51 8,53	$C_{19}H_{23}NO$	81,10	8,68	60,6
IX	170—175 (1,5)	74—76 (From alcohol)	1,5813	80,81 80,71	7,95 7,82	$C_{18}H_{21}NO$	80,86	7,92	24
X	182—183 (1)	—	1,5935	76,47 76,29	7,51 7,63	$C_{18}H_{21}NO_2$	76,29	7,47	63
XI	192—197 (1,5)	—	1,5785	76,81 77,09	7,89 7,95	$C_{20}H_{25}NO_2$	77,13	8,09	17,5
XII	204—205 (2)	—	1,5990	81,07 81,12	7,59 7,70	$C_{18}H_{21}NO$	80,86	7,92	17,2
XIII	—	173—174 (From methanol)	—	72,39 72,21	6,67 6,89	$C_{18}H_{19}NO_3$	72,70	6,44	25,2
XVII	140,5—141 (1)	60—61 (From hexane)	—	73,45 73,32	7,06 6,94	$C_{15}H_{17}NO_2$	74,04	7,04	36

* Yield based on the anil that reacted.

TABLE 3. Characteristics of Quinolines Obtained

Cpd. No.	B. p., °C (p, mm)	M. p., °C	M. p. of picrate, °C	Data in literature		Lit. ref.
				m.p. of quinoline, °C	m. p. of picrate, °C	
Va	140—142 (2)	82—83 (From hexane)	187—188	82—83	187—188	18
VIa	144—145 (1,5)	—	206,5—207	—	205	19
VIIa	150—160 (1,5)	—	209—210	—	212—213,5	20
Xa	180—190 (2)	129—130	206—207	133	205	21
XIIIa	—	157—158 (From methanol)	—	158—159	—	22
XVIIa	120—123 (1,5)	87—88 (From hexane)	187—188	92	186	25

10% NaOH solution and dried over K_2CO_3. In the fractionation, which was accompanied by decomposition, we obtained 7 g (69%) of a fraction of b. p. 167-170° (1.5 mm), which crystallized on standing. The fraction consisted of 2-phenylquinoline (Va), probably containing 1,2-dihydro-2-phenylquinoline impurity. From it we prepared the picrate of (Va).

8-Methyl-2-phenylquinoline (XIIa). $KMnO_4$ powder was added in portions with vigorous stirring to a solution of 1 g of 4-ethoxy-1,2,3,4-tetrahydro-8-methyl-2-phenylquinoline (XII) in 30 ml of acetone. The mixture was left overnight, after which the precipitate was filtered off. Solvent was driven off, and we obtained 0.7 g of (XIIa) as an orange liquid, which we were unable to crystallize. From it we prepared the picrate of (XIIa), m. p. 126-128°. Found: C 58.83; 58.63; H 3.86; 3.88%. $C_{22}H_{16}N_4O_7$. Calculated: C 58.93; H 3.60%.

2-o-Nitrophenylquinoline (XIV). To a solution of 31.6 g of N-o-nitrobenzylideneaniline in 100 ml of dry benzene we added 1 ml of BF_3 etherate and 12.2 g of ethyl vinyl ether. The temperature of the reaction mixture rose from 18.5 to 40.5°. The mixture was stirred for 3 h, after which it was treated in the usual way. In the fractionation, which was accompanied by decomposition, we isolated 3.7 g (13%) of (XIV), b. p. 187-190° (0.2 mm), m. p. 118.5-119.5° (from alcohol). Found: C 70.98; 71.06; H 3.95; 4.13%. $C_{15}H_{10}N_2O_2$. Calculated: C 71.99; H 4.03%. Picrate, m. p. 176-178°. Found: C 52.76; 52.76; H 2.91; 3.27%. $C_{21}H_{13}N_5O_9$. Calculated: C 52.62; H 2.74%.

3-Phenylbenzo[f]quinoline (XV). To 74.8 g of N-benzylidene-2-naphthylamine dissolved in 200 ml of dry benzene we added 0.5 g of BF_3 etherate and then 31 g of ethyl vinyl ether. In a short time reaction set in, and the temperature of the mixture rose to 63°. The mixture was then left for three days. On dilution of the mixture with hexane we isolated 15.5 g (20%) of (XV), m. p. 187-188°. The literature [23] gives m. p. 188°.

4-Ethoxy-1,2,3,4-tetrahydro-2-phenylbenzo[h]quinoline (XVI) and 2-Phenylbenzo[h]quinoline (XVIa). To a solution of 23 g of N-benzylidene-1-naphthylamine in 100 ml of dry benzene we added 0.25 ml of BF$_3$ etherate and then 11 g of ethyl vinyl ether. The temperature of the reaction mixture rose from 25 to 37°. The reaction mixture was stirred for 4.5 h and then treated in the usual way. On fractionation we obtained 4.8 g (19% yield based on adduct) of a fraction with b. p. 200-220° (1.5 mm), the analysis of which corresponded to a mixture of (XVI) and (XVIa). The spectrum of this fraction contained an NH absorption band at 3420 cm^{-1}, but it was weak and diffuse. Part of this fraction (1.9 g) was dissolved in 50 ml of acetone and treated with 3 g of KMnO$_4$ powder. The MnO$_2$ precipitate was separated, solvent was driven off, and we obtained 1.5 g of (XVIa), m. p. 66-67° (from alcohol). Picrate, m. p. 163-164°. For (XVIa) the literature [24] gives: base, m. p. 68°; picrate, m. p. 167°.

SUMMARY

1. Schiff bases react with alkyl vinyl ethers in presence of Lewis acids (BF$_3$, AlCl$_3$, AlBr$_3$) by the diene synthesis scheme with formation of 4-alkoxy-2-aryl-1,2,3,4-tetrahydroquinolines.

2. Under the action of p-toluenesulfonic acid or of oxidizing agents 4-alkoxy-2-aryl-1,2,3,4-tetrahydroquinolines are converted into the corresponding 2-arylquinolines.

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