

## HYDROXYMETHYLATION AND ALKYLATION OF COMPOUNDS OF THE FURAN, THIOPHENE, AND PYRROLE SERIES IN THE PRESENCE OF H<sup>+</sup> CATIONS (Review)\*

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*Published data and the results of the authors' own investigations on the transformations of O-, S-, and N-heterocyclic compounds under the conditions of acid-catalyzed hydroxymethylation and alkylation are summarized. The mechanisms and the directions of the reactions taking place under the influence of weakly and strongly acidic ion exchangers are discussed.*

### 1. INTRODUCTION

Acid-catalyzed reactions leading to the formation of C—C bonds (hydroxymethylation with formaldehyde, alkylation with various agents) are extremely difficult to realize in heterocyclic compounds (e.g., furan, pyrrole). This is due to the acidophobic nature of these series of compounds, leading to their considerable resinification under the influence of the soluble strong acids usually employed as catalysts in these processes. As a result, it is impossible to obtain high yields. Table 1 shows published data from study of the reactions of furan compounds with formalin (a 35-36% aqueous solution of formaldehyde) in the presence of catalysts (strong soluble acids). Two types of compound (the respective alcohol and/or methane derivatives) are formed in the reactions of furan and sylvane with formaldehyde. The yield of 2,2'-difurylmethane in the reaction of furan with formalin, catalyzed by HCl, amounted to 2% and was increased to 45% when furan was reacted with furfuryl alcohol instead of formaldehyde. On this basis it was assumed that during the reactions of furan compounds with formaldehyde the respective alcohols are intermediates in the formation of difurylmethanes [3].

At the beginning of the 1980s, experiments were carried out [4] in which the furan derivative 5-hydroxymethylfurfural was obtained with a yield of up to 66% from D-fructose with an H<sup>+</sup> ion exchanger as catalyst. This illustrates the prospects of using acidic cation exchangers for syntheses in such heterocyclic acidophobic compounds. The use of insoluble polymeric ion-exchange resins as catalysts has many advantages; they can be separated from the reaction mixtures by simple filtration, are easily regenerated, and can be used repeatedly without loss of activity [5, 6]. Recently, cation exchangers in the H<sup>+</sup> form were used successfully as acidic catalysts in various processes of fine organic synthesis [7-11]. In particular, H<sup>+</sup> ion exchangers have been used in the Prins reaction (the condensation of alkenes with formaldehyde); here the role of the cation exchanger is to activate the formaldehyde molecule as a result of protonation with the formation of the carbocation [CH<sub>2</sub>OH]<sup>+</sup>, the counterion of which is a polymeric anion [12-15]. In these papers it was shown that the catalytic properties are affected both by the nature of the functional acid group (—SO<sub>3</sub>H, —COOH) and by the structure of the polymeric matrix. Weakly acidic polyacrylic carboxylic cation exchangers have low activity in the reaction of styrene with CH<sub>2</sub>O — the yield of the condensation product amounted to only 4%. At the strongly acidic polystyrene sulfo cation exchangers yields of 15-92% were obtained, depending on the degree of cross linking, the exchange capacity, and other parameters of the employed resins [13, 14]. Microporous styrenedivinylbenzene sulfo cation exchangers are rather more effective than the gel type in the Prins reaction, but in this case the degree of cross linking has little effect on the catalytic characteristics [15].

\*The authors consider it their duty to mention that the work on the review was initiated by Prof. M. V. Shimanskaya.

TABLE 1. Reaction of Furan and Sylvane with Formaldehyde, Catalyzed by Inorganic Acids [1-3]

Substrate	Catalyst	Reaction product	Yield, %
Furan	HF	Di(2-furyl)methane	14
Sylvane	H <sub>3</sub> PO <sub>4</sub>	Bis(5-methyl-2-furyl)methane	40
Furan	HCl	Furfuryl alcohol	15
		Di(2-furyl)methane	2
Sylvane	HCl	Bis(5-methyl-2-furyl)methane	34

TABLE 2. Characteristics of the Employed Cation-Exchange Resins [25, 26]

Resin	Functional group	Exchange capacity, mg-eq H <sup>+</sup> /g	pK <sub>a</sub>	Porosity of polymeric matrix (copolymer)	Grain size, mesh	Internal specific area, m <sup>2</sup> /g
Amberlyst 15 (1)	-SO <sub>3</sub> H	4,6	<1-2	Macroporous (styrene-DVB*)	20...50	>50
Dowex 50W × 4 (2)	-SO <sub>3</sub> H	5,0	<1-2	Macroporous (styrene-DVB)	100...200	<0,1
Amberlite IRC-50 (3)	-COOH	10,0	6,1	Macroporous (methacrylic acid-DVB)	16...50	—
Amberlite IRC-84 (4)	-COOH	10,0	5,3	"Gel" type (cross-linked acrylic)	20...50	—

\*DVB is divinylbenzene.

Until recently there have been no data in the literature on the use of ion exchangers in transformations of heterocyclic compounds. Only in the 1980s and 1990s were researches carried out [16-24] with various H<sup>+</sup> cation exchange resins during hydroxymethylation and alkylation in the furan, thiophene, and pyrrole series. In the present review, the results of these investigations are summarized and the method is compared with other methods that have been described for the synthesis of the desired heterocyclic compounds.

## 2. HYDROXYMETHYLATION OF FURAN COMPOUNDS

Investigations were carried out into the reactions of furan, sylvane, furfural, 2,5-dimethylfuran, and furfuryl alcohol with formalin in the presence of H<sup>+</sup> cation exchangers (Table 2), differing in the nature and porosity of the polymeric matrix, the strength of the acid groups, the exchange capacity, and other parameters. The sulfo cation exchangers Amberlyst 15 (1) and Dowex 50W × 4 (2) are characterized by similar values for the exchange capacity and acidity but differ in the porosity of the polymeric matrix. Both these cation exchangers are of the strongly acidic type ( $pK_a$  in water  $\leq 1-2$  [26]). For the resin (1) dispersed in water, a more suitable characteristic of the acidity (the Hammett acidity function  $H_0$ ) was determined by the SINA method (sorption of indicators for the determination of the acidity of solid materials), as used for strong acids. The obtained result was  $-2.15$  to  $-2.18$ , which corresponds to the acidity of 35-38% aqueous sulfuric acid [27]. The macroporous ion exchanger (1) is characterized by high values for the internal specific surface area ( $> 50$  m<sup>2</sup>/g); the acid centers of this copolymer are accessible even without swelling of the resin [28]. The microporous sulfo cation exchanger (2) has considerably lower specific surface area ( $< 0.1$  m<sup>2</sup>/g). The accessibility of the acid centers in this ion exchanger depends on a series of factors, including the ability to swell in the employed solvent [28]. The carboxylic cation exchangers Amberlite IRC (50 and 80) are weakly acidic ( $pK_a$  5.3-6.1) but differ in the structure of the polymeric matrix. As follows from numerous published data [4-15], weakly acidic carboxylic cation exchangers have been investigated as catalysts considerably less than the strongly acidic sulfo cation exchangers.

TABLE 3. Characteristics of the Preparative Syntheses

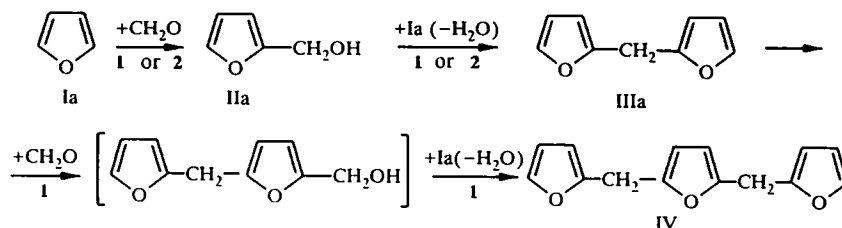
Synthesized compound	Initial compounds, molar ratio	Catalyst (mole %)	Reaction time, h	Preparative yield, mole %
IIa	Ia-CH <sub>2</sub> O, 1 : 2,5	1 (5)	5	81
IIIa	IIa-Ia, 1 : 2	1 (5)	5	60
IIb	Ib-CH <sub>2</sub> O, 1 : 3	3 (50)	68	85
IIIb	Ib-CH <sub>2</sub> O, 1 : 3	1 (10)	1	80
V	Ic-H <sub>2</sub> O, 1 : 15	1 (10)	72	93
VI	IIa-CH <sub>2</sub> O, 1 : 3	3 (30)	120	28
IIc	Id-CH <sub>2</sub> O, 1 : 2	1 (5)	0,25	55
VII	Ie-CH <sub>2</sub> O, 1 : 20	1 (25)	48	60
IIIc	If-CH <sub>2</sub> O, 1 : 20	1 (25)	12	75

TABLE 4. Alkylation of Furan (Ia), Thiophene (Ig), Pyrrole (Ih), and N-Methylpyrrole (Ii) with *tert*-Butyl Alcohol in the Presence of Cation Exchanger Amberlyst 15

Heterocycle	Solvent (concentration, M)	Heterocycle <i>t</i> -butanol-H <sup>+</sup> molar ratios	<i>T</i> , °C	Time, h	Reaction product (yield according to GLC), ratio of reaction products
Ia	—	7,5 : 1 : 1,15	20...25	24	IX (80)
IX	—	4 : 1 : 2,15	20...25	24	X (75)
Ig	—	7,5 : 1 : 1,15	80	1	XII + XIII (~100), XII—XIII, 3,5 : 1
Ia	CCl <sub>4</sub> (0,3)	1 : 1,5 : 2	76	3	IX (90)
Ia	CCl <sub>4</sub> (0,3)	1 : 1,5 : 20	20...25	0,5	IX + X (~100), IX—X, 1 : 3,5
Ih	—	1 : 3 : 0,1	80	12	XIV + XV (~70) + XVI (~10), XIV—XV, 1,7 : 1
Ii	—	1:30:2,5	80	8	XVII+XVIII (82) + XIX (~10), XVII—XVIII, 1,4:1

Furfuryl alcohol (IIa) (yield up to 95%, according to GLC) and also di(2-furyl)methane (IIIa) and 2,5-bis(2-furylmethyl)furan (IV) with yields up to 13 and ~10% respectively were found among the products from the reaction of the furan (Ia) with formaldehyde at room temperature in the presence of cation exchangers (1-4) with various of the furan, formaldehyde, and catalyst.

Among the investigated cation-exchange resins, the most active catalyst was the strongly macroporous sulfo cation exchanger (1). Somewhat less active was the microporous sulfo cation exchanger (2), while the weakly acidic carboxylic cation exchangers were almost completely inactive. This demonstrates the important role of protonation in the investigated process. The higher activity of (1) compared with (2) is clearly explained by the somewhat higher acidity of the macroporous sulfo cation exchangers compared with the microporous materials, as demonstrated in [28]. On the basis of the dependence of the yields of compounds (IIa, IIIa, IV) on the reaction conditions and on the reaction time, it is possible to propose the following scheme for their formation:

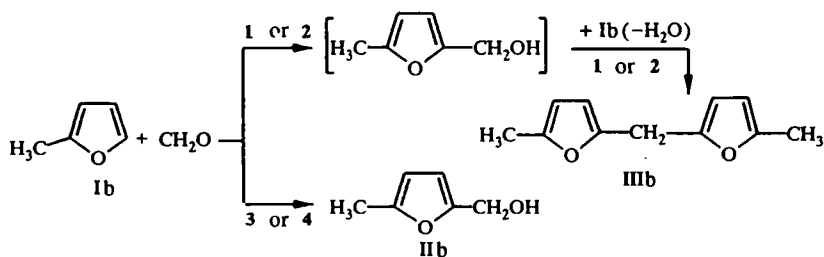


The conditions under which it was possible to obtain a high yield of the alcohol (IIa) were found. For this purpose it is necessary to use the highly acidic macroporous sulfo cation exchanger (1) at the rate of 5-10% (with reference to H<sup>+</sup>) on

the substrate. The optimum (Ia)–formaldehyde ratio is 1:2.5-3. It is not possible to synthesize compound (IIIa) with a sufficiently high yield by the reaction of furan with formaldehyde under the investigated conditions. In order to produce compound (IIIa) the alcohol (IIa) was reacted with furan in the presence of the cation exchanger (1), where the yield of (IIIa) amounted to 65% (according to GLC).

In the reaction of sylvane (Ib) with formalin at room temperature in the presence of the sulfo and carboxy cation exchangers (1-4), 5-methyl-2-hydroxymethylfuran (IIb) with a yield up to 90% (GLC) and bis(5-methyl-2-furyl)methane (IIIb) with a yield up to 95% were detected in the reaction products. Their ratios depended on the reaction conditions. The ion-exchange resins can be arranged according to their activity in the order (1)  $\geq$  (2)  $\gg$  (4)  $>$  (3), corresponding to the order of variation in their acidity. It is important to note that the hydroxymethylation of sylvane (in contrast to furan) is catalyzed not only by the strongly acidic sulfo cation exchangers (1) and (2) but also by the weakly acidic ion exchangers (3) and (4). This is probably due to the greater nucleophilicity of sylvane compared with furan.

It is seen from the obtained results that difurylmethane (IIIb) is formed as a result of further transformations of the alcohol (IIb). The methane derivative (IIIb) is mainly formed in the presence of the strongly acidic cation exchangers (1) and (2) (with all the investigated ratios of the reagents). In the presence of weakly acidic cation exchangers (3) and (4), the process takes place slowly, and the alcohol (IIb) is formed almost exclusively. The latter only undergoes further transformation to a small degree. Thus, the sulfo cation exchangers (1) and (2) protonate both formaldehyde and the alcohol (IIb) [like the alcohol (IIa)], whereas the acidity of the carboxylic cation exchangers is high enough for the protonation of formaldehyde but too low for the protonation of the alcohol (IIb). The reaction of sylvane with formaldehyde in the presence of various cation exchangers can be represented by the following scheme:



Conditions were found under which it was possible to obtain high yields (90-95%, GLC) of the alcohol (IIb) or the methane derivative (IIIb). For the selective production of the alcohol (IIb) the cation exchanger (3) was used with an excess of formaldehyde [(Ib)–formaldehyde–H<sup>+</sup> ratios 1:3:0.5]. The synthesis of (IIIb) must be conducted in the presence of the cation exchanger (1) in an excess of sylvane [(Ib)–formaldehyde–H<sup>+</sup> ratios 10:0.1:0.1]. The developed method for the synthesis of the alcohol (IIb) (which is a valuable synthon but is at present difficult to obtain) may compete with known methods for its production by the reduction of methyl 5-methylfuran-2-carboxylate (yield 86%) [29] or methylfurfural (yield 96%) [30] with lithium aluminum hydride or by catalytic reduction of the respective compounds with hydrogen at a nickel–chromium catalyst (yield 81%) [30] or an oxide copper–chromium catalyst deposited on carbon (yield 95%) [31]. The yield of the alcohol (IIb), obtained by hydroxymethylation of sylvane, was close to the value indicated in the literature. However, the method was much simpler and did not require the use of a special catalyst, elevated temperature, or the inflammable lithium aluminum hydride. A method is also known for the production of the alcohol (IIb) from furfural by the Cannizzaro reaction by the action of an aqueous solution of sodium hydroxide, but the yield of the desired product here amounted to only 30% [32]. The only disadvantage of the method for the synthesis of the alcohol (IIb) by the hydroxymethylation of sylvane in the presence of cation exchanger 3 is the fairly long reaction time — almost three days at 20-25°C. (It is not possible to increase the temperature on account of the increase in the yield of resinification products and the products from hydrolysis of the sylvane.)

Difurylmethane (IIIb) was obtained with a high yield by the reaction of sylvane with formaldehyde in the presence of the strongly acidic cation exchangers (1) and (2). [This is in contrast to compound (IIIa), for the synthesis of which it was necessary to use the reaction of the alcohol (IIa) with furan.] The obtained yield of compound (IIIb) (95% according to GLC) was considerably higher than those obtained in the literature (40% [2] and 34% [3]) and also by the reaction of sylvane with formaldehyde but in the presence of other acidic catalysts (Table 1). Difurylmethane (IIIb) is a liquid with a pleasant anise odor and can be used in perfumery [2].

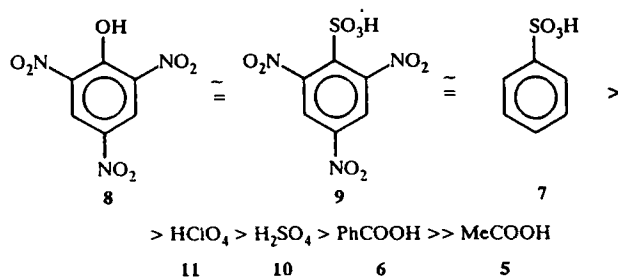
TABLE 5. Reaction of Furfuryl Alcohol (IIa) with Furan (Ia), Thiophene (Ig), and Pyrrole (Ih) in the Presence of the Cation Exchanger Amberlyst 15

Substrate	Molar ratios (IIa)-sub- strate-H <sup>+</sup>	<i>t</i> , °C	Time, h	Conver- sion of (IIa), %	Reaction product (yield according to GLC, %)
Ia	1 : 2 : 0,05	20...25	5	70	IIIa (65), IV (1...2)
Ig	1 : 3 : 0,2	20...25	15	100	IIIg (47), IVa (22)
Ih	1 : 3 : 0,2	100	28	90	IIIh' (62), IIIh'' (~10), IVa (6)

TABLE 6. Characteristics of the Alkylation of Heterocycles by Alcohols in the Presence of the Sulfo Cation Exchanger Amberlyst 15

Alkylating agent	Heterocycle	Reaction temperature, °C	Ratio of yields of 2- and 3-isomers in alkylation products
<i>tert</i> -Butyl alcohol	Furan	20...25	1 : 0
	Thiophene	80	3,5 : 1
	Pyrrole	80	1,7 : 1
Furfuryl alcohol	Furan	20...25	1 : 0
	Thiophene	20...25	1 : 0
	Pyrrole	100	6,2 : 1

In order to determine the mechanism of the reaction of sylvane with formaldehyde, this reaction was also studied in the presence of a series of soluble organic and inorganic acids (5-11) with various strengths and lipophilicities. The results were compared with the data obtained during hydroxymethylation at H<sup>+</sup> cation exchangers. The reaction mixtures were diluted with chloroform [10 vol. % of (Ib) in chloroform] with (Ib)-formaldehyde-H<sup>+</sup> molar ratios of 1:1.5:0.05 at room temperature. The rates of formation of compounds (IIb) and (IIIb) for small degrees of transformation (up to 10%) were calculated. The results confirm that the activity of the cation exchangers (1-3) in hydroxymethylation is proportional to their acidity. The investigated acids vary in the following order according to the overall rate of hydroxymethylation:

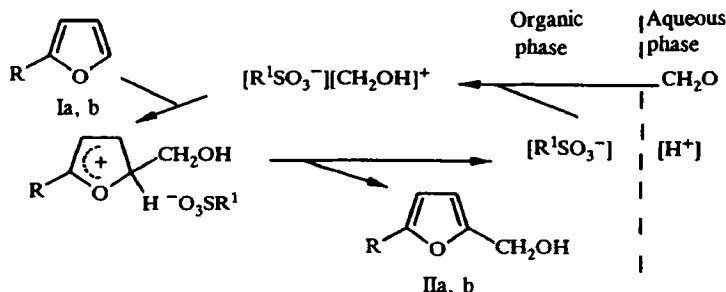


On examination of this series it is seen that two factors are important for the catalytic activity of the acid in hydroxymethylation in the two-phase system consisting of an organic phase (chloroform-sylvane) and an aqueous phase (water-formaldehyde), i.e., the strength of the acid and its lipophilicity. The most active in the investigated process are the fairly strong lipophilic aromatic acids (7)-(9). The rates of hydroxymethylation in their presence are similar, since these catalysts differ little in acidity and lipophilicity. The activity of the inorganic acids (10, 11) is somewhat lower, in spite of the higher acidity, on account of their lower lipophilicity. Here the reaction rate correlates with the *pK<sub>a</sub>* values of these acids. The least active are the weak acids (5, 6) and, particularly, the hydrophilic acetic acid. Experiment showed that the activity of a mixture of benzoic and sulfuric acids is higher than for each of them in isolation, since such a mixture provides high acidity for protonation and sufficient lipophilicity for the transfer of the cations into the organic phase.

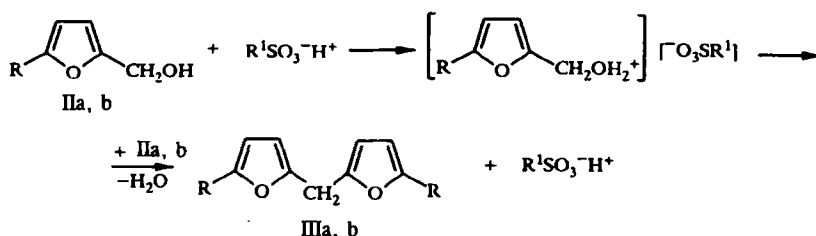
*p*-Toluenesulfonic acid is somewhat more active higher than the cation exchangers containing the SO<sub>3</sub>H function. It is clear that this is due to the lower acidity of the sulfo cation exchangers compared with the soluble analogs [28]. In spite of the high activity, the soluble acids (7-9) cannot be recommended as catalysts for hydroxymethylation on account of rapid resini-

fication of the acidophobic furan compounds under the influence of these strong lipophilic acids. This is much less characteristic of the cation exchangers (1, 2).

It can thus be supposed that the mechanism of the hydroxymethylation of furan and sylvane to alcohols under the influence of the active acidic catalysts includes protonation of the formaldehyde, dissolved in water, and transfer of the obtained cation into the organic phase as a result of the formation of an ion pair with the lipophilic anion of the catalyst; normal electrophilic substitution then takes place in the organic phase, resulting in the formation of the alcohol (IIa, b), and the catalyst is regenerated, as shown in the scheme (for catalysis by the lipophilic sulfonic acids):



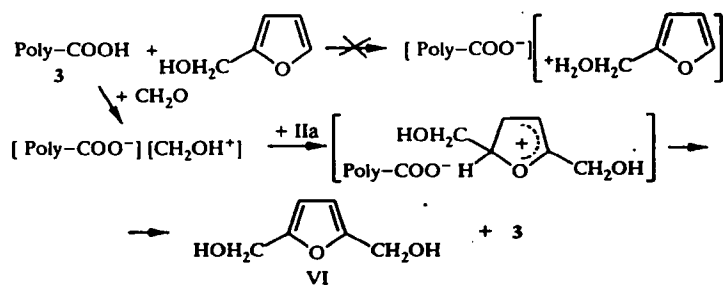
In the presence of strong acids, the transformation to the methane derivatives (IIIa, b) takes place through the protonation of the obtained alcohols (IIa, b), probably according to the following scheme:



Attempts at the hydroxymethylation of furfural by the action of formalin in the presence of cation exchangers (1-4) were unsuccessful. Only traces of 5-formyl-2-furfuryl alcohol were detected in the catalyzates [in the presence of resin (1)].

Hydroxymethylation products were not detected in the reaction of formalin with 2,5-dimethylfuran (Ic) in the presence of the cation exchanger (1) — only acid hydrolysis of compound (Ic) to 2,5-hexanedione (V) occurred. With an excess of water compound (V) is formed under these conditions with an almost quantitative yield. A test showed that the substrate (Ic) is completely hydrolyzed by water in the presence of the catalyst (1) giving a 95% yield (according to GLC) of compound (V). This agrees with data in [33], where the dione (V) was produced by the hydrolysis of compound (Ic). [In the presence of acetic and sulfuric acids with boiling for 36 h the yield of the dione (V) amounted to 86-90%.]

One valuable derivative of furan is 2,5-di(hydroxymethyl)furan (VI), used as intermediate in the production of medicinal [34] and crown compounds [35]. Several methods are known for the production of compound (VI). The dicarbinol (VI) was obtained with a 35% yield from the acetate of furfuryl alcohol in two stages, i.e., by the action of paraform in acetic acid and then by the action of sodium on the obtained diacetate in acetic anhydride [36]. Compound (VI) was also synthesized with a 90-96% yield from the difficultly obtainable 5-formyl-2-furfuryl alcohol by reduction with sodium amalgam [37] or with hydrogen under a pressure of 100 atm at 140°C at a copper-chromium catalyst [38]. The production of the dialcohol (VI) in a single stage from the readily available furfuryl alcohol by hydroxymethylation with formaldehyde is an extremely attractive method. However, this process cannot be realized in the presence of strong acids on account of a competing reaction, i.e., the protonation of the carbinol group of furfuryl alcohol and its further transformation into the condensation products. Since it was found that protonation of the alcohols (IIa, b) does not take place under the influence of the weakly acidic cation exchangers (3, 4) (while the formaldehyde is protonated), the possibility of hydroxymethylating the alcohol (IIa) with formaldehyde in the presence of these catalysts arose. In fact, the dialcohol (VI) is formed in the reaction of the alcohol (IIa) with formaldehyde in the presence of the ion-exchange resin (3), presumably according to the following scheme:



The optimum conditions for this reaction were found: room temperature, (IIa) – formaldehyde –  $H^+$  ratios 1:2-5:0.2-0.5. Under these conditions, the alcohol (IIa) was converted fully into the diol (VI) after stirring for five days. The yields were 25-30%. Data on the preparation of compounds (IIa, b, IIIa, b, V, VI) are given in Table 3.

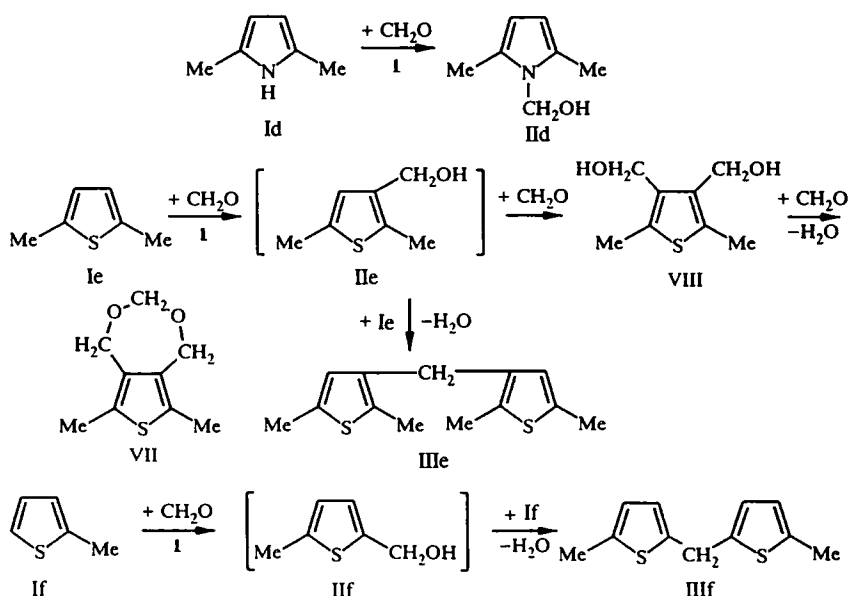
Thus, investigations into the reaction of furan compounds with formaldehyde in the presence of acidic catalysts make it possible to reach the following basic conclusions.

1. With strongly and weakly acidic cation exchangers as catalysts for the hydroxymethylation of furan compounds, it is possible to avoid their resinification completely and to obtain good yields of furfuryl alcohols or bis(furyl)methanes; the direction of the transformation is determined by the acid strength of the cation exchanger.

2. The rate of formation of the alcohols from the furan compounds increases with increase in the strength and lipophilicity of the acidic catalysts. Such relationships indicate that the mechanism of hydroxymethylation includes protonation of the formaldehyde and phase transfer of the hydroxymethyl cation as intermediate processes.

### 3. HYDROXYMETHYLATION OF METHYL-SUBSTITUTED PYRROLE AND THIOPHENE IN THE PRESENCE OF $H^+$ CATION EXCHANGERS

The acid-catalyzed processes involved in the reaction of unsubstituted furan, thiophene, and pyrrole with formalin take place by a mechanism of electrophilic aromatic substitution at position 2 of all these heterocycles [1, 3, 39, 40]. In contrast, the 2,5-dimethyl derivatives of pyrrole (Id) and thiophene (Ie) react at different positions of the rings during reaction with formaldehyde in the presence of the cation exchanger (1). Thus, dimethylpyrrole (Id) is hydroxymethylated at the nitrogen atom of the ring with the formation of 2,5-dimethyl-1-hydroxymethylpyrrole (IId). The reaction of (Id) with dimethylthiophene takes place at positions 3 and 4 of the ring with the formation of 1,3-dioxacycloheptano[5,6-c]-2,5-dimethylthiophene (VII) as the main product. During the hydroxymethylation of 2-methylthiophene, a high yield of bis(5-methyl-2-thienyl)methane (IIIe) was obtained. The weakly acidic cation exchanger (3) does not catalyze these reactions.



In the presence of the sulfo cation exchanger (1), the reaction with the pyrrole (Id), as the most reactive among the investigated heterocyclic compounds, takes place quickly; after 10-15 min the degree of transformation amounts to 70-75%, while the yield of the alcohol amounts to approximately 60% (according to GLC). In order to prevent subsequent polymerization it is necessary only to filter off the cation exchanger.

During the hydroxymethylation of compound (Ie), the thiophene alcohols 2,5-dimethyl-3-hydroxymethylthiophene (IIe) and 2,5-dimethyl-3,4-di(hydroxymethyl)thiophene (VIII) and also the product from intermolecular dehydration bis(2,5-dimethyl-3-thienyl)methane (IIIe) were detected by chromato-mass spectrometry in addition to the main compound (VII). The diol (VIII) was isolated by preparative HPLC.

In the reaction with 2-methylthiophene, the intermediate product 5-methyl-2-hydroxymethylthiophene (IIIf) was also detected. Data on the preparative synthesis of compounds (IIId, VII, IIIIf) are given in Table 3.

#### 4. ALKYLATION OF FURAN, THIOPHENE, AND PYRROLE BY ALCOHOLS IN THE PRESENCE OF CATION EXCHANGER AMBERLYST 15

The use of traditional Friedel–Crafts alkylation in the case of five-membered heterocycles is greatly restricted on account of the acidophobic nature of these compounds [41, 42]. The use of H<sup>+</sup> cation exchangers, whose acid strength would make it possible to protonate the corresponding alcohols, is promising for the production of alkylation products in heterocyclic compounds. As described above, furfuryl alcohol is protonated at the strongly acidic sulfo cation exchanger Amberlyst 15 (1). Experiments showed that the cation exchanger (1) also protonates *tert*-butyl alcohol (but does not protonate, for example, 2-propanol or benzyl alcohol, at least in reactions with furan and sylvane). These data made it possible to use the alkylation of five-membered heterocycles by *tert*-butyl and furfuryl alcohol in the presence of the cation exchanger (1) for the synthesis of *tert*-butyl and furfuryl derivatives of furan, thiophene, and pyrrole.

##### 4.1. Alkylation with *tert*-Butyl Alcohol

The usual methods for the synthesis of the *tert*-butyl derivatives of heteroaromatic compounds are laborious multistage processes and frequently give low yields of the desired compounds. The best of the methods known until recently for the synthesis of 2-(*tert*-butyl)furan (IX) (with a yield of 67%) is the alkylation of furan-2-carboxylic acid by *tert*-butyl chloride in the Friedel–Crafts reaction followed by decarboxylation of the obtained 5-(*tert*-butyl)furan-2-carboxylic acid in the presence of quinoline and copper oxide at 220°C [43]. A method was proposed for the alkylation of aromatic and heterocyclic compounds with *tert*-butyl bromide catalyzed by silica gel. In the case of furan and thiophene, only the corresponding 2,5-di(*tert*-butyl) derivatives (X, XI) were obtained, and the monoalkyl derivatives were not formed [44]. A mixture of 2- and 3-(*tert*-butyl)thiophenes (XII, XIII) was obtained with a 74% yield during the action of *tert*-butyl chloride in the presence of aluminum chloride in methylene chloride at –70°C. According to GLC and PMR, the ratio of the 2- and 3-isomers amounted to (83-85):(15-17) [45, 46].

The action of the Grignard reagent (RMgBr) on pyrrole followed by alkylation of the obtained N-pyrrolylmagnesium bromide with *tert*-butyl chloride or *tert*-butyl bromide gave 2-(*tert*-butyl)pyrrole (XIV) with a yield up to 33% and 3-(*tert*-butyl)pyrrole (XV) with a yield up to 18%; up to 10% of di(*tert*-butyl)pyrroles (XVI) was also formed [47, 48]. The Friedel–Crafts alkylation of pyrrole with *tert*-butyl chloride in methylene chloride at –80°C in the presence of aluminum chloride gave compounds (XIV) and (XV) with yields of 15 and 11% respectively [49]. Other methods for the synthesis of compounds (XIV, XV) with higher yields but from less readily available compounds than pyrrole have also been described [50].

Thus, the complexity and the inadequacy of existing methods for the synthesis of the *tert*-butyl derivatives of five-membered aromatic heterocycles has led to the need to develop new simple methods of synthesis.

Table 4 gives the results obtained during investigation of the reaction of furan (Ia), thiophene (Ig), pyrrole (Ih), and N-methylpyrrole (Ii) with *tert*-butanol in the presence of the cation exchanger (1). When the reaction was carried out in an excess of furan, compound (IX) was obtained with a yield of 80% (according to GLC) calculated on the *tert*-butanol. Under analogous conditions, compound (IX) is alkylated to the dialkyl derivative with a yield of 75%. *tert*-Butylation of thiophene does not occur at room temperature, but at 80°C a 3.5:1 mixture of compounds (XII, XIII) is formed with a quantitative yield after 1 h.

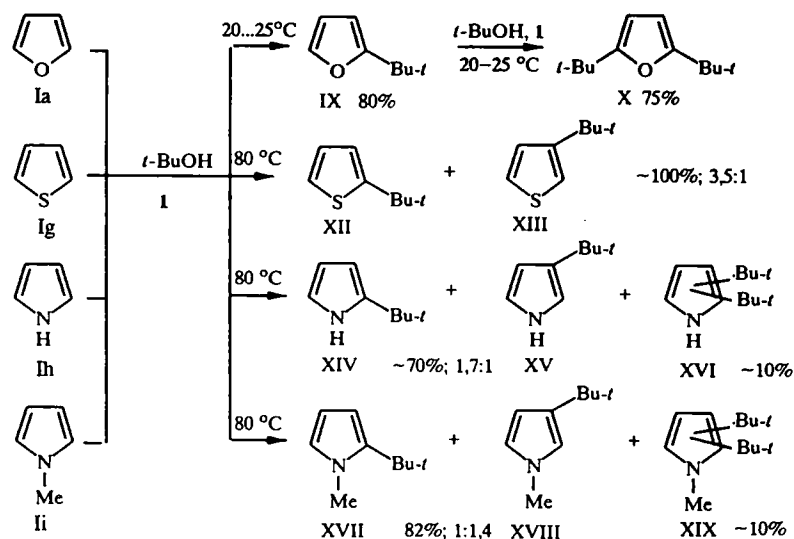


If the reaction with furan is conducted in the inert solvent carbon tetrachloride (0.3 M) with (Ia)–*t*-butanol–H<sup>+</sup> ratios of 1:1.5:2 at 76°C, compound (IX) is formed with a yield of 90%. A tenfold increase in the amount of the cation exchanger (1) accelerates the reaction considerably, and at room temperature it is complete in 30 min and gives a 1:3.5 mixture of the products (IX) and (X).

Table 4 gives the obtained optimum conditions for the alkylation of pyrrole: reagent ratios (Ih)–*t*-butanol–H<sup>+</sup> 1:3:0.1, temperature 80°C. Here the reaction is complete in 12 h with the formation of the products (XIV, XV) (total yield ~70% according to GLC) and two isomers of the dialkyl derivatives (XVI) each with a yield up to 5%. The ratios of compounds (XIV-XV) amount to (1.6-1.7):1. The preparative yield of the mixture of isomers amounts to 62% on the initial pyrrole. The individual compounds (XIV, XV) were isolated by preparative GLC by analogy with the methods in [48, 50].

In spite of the high basicity of *N*-methylpyrrole compared with pyrrole, the alkylation of the methyl derivative takes place under harsher conditions [a considerable excess of *tert*-butanol and the cation exchanger (1), Table 4]. The main products are 2- and 3-*tert*-butyl-*N*-methylpyrroles (XVII) and (XVIII) respectively, which were obtained for the first time with an overall yield up to 82% (GLC). However, the 3-isomer predominates [(XVII):(XVIII) ratio 1:1.4]. The reasons for the position selectivity of the reactions of heterocyclic compounds with electrophiles remain unexplained; for five-membered heterocycles in many electrophilic reactions this characteristic decreases in the order furan > thiophene > pyrrole [51]. This series was confirmed completely in the reaction with *tert*-butanol in the presence of Amberlyst 15. Furan is only *tert*-butylated at the  $\alpha$  position, 2- and 3-*tert*-butylthiophenes (ratio 3.5:1) are formed from thiophene, and the 2- and 3-*tert*-butylpyrroles obtained in the synthesis are in a ratio of 1.7 to 1 (i.e., preferential 2-substitution is observed). In the case of the *tert*-butylation of *N*-methylpyrrole, the position selectivity is minimal (30-40%), and the 3-isomer predominates. Quantum-chemical calculations [24] showed that the position selectivity (like, also, the reduced reactivity) is due mainly to steric hindrances created by the N-CH<sub>3</sub> group more at the neighboring position 2 than at position 3.

The *tert*-butylation of five-membered heterocycles in the presence of the cation exchanger (1) can be represented by the following scheme:



## 4.2. Alkylation with Furfuryl Alcohol

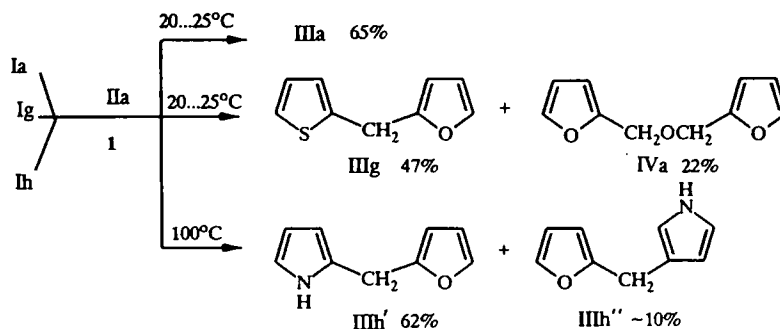
As shown above, the reaction of furan (Ia) with furfuryl alcohol (IIa) in the presence of the cation exchanger (1) leads to the formation of 2,2'-difurylmethane (IIIa). Apart from furan, the reaction of the alcohol (IIa) with thiophene (Ig) and pyrrole (Ih) was also studied with the reagents (IIa), (Ia) [or (Ig, h)], and H<sup>+</sup> in molar ratios of 1:(1-5):(0.05-0.5) in the range of temperatures between room temperature and 100°C. The reactivity of thiophene in reaction with the alcohol (IIa) under the investigated conditions is lower than that of furan. The main reaction product is 2-furyl-2-thienylmethane (IIIg); in addition, significant amounts of 2,2'-difurfuryl ether (IVa) are formed. Increased temperature is necessary for the alkylation of pyrrole. The two isomeric compounds 2-furyl-2-pyrrolylmethane (IIIh') and 2-furyl-3-pyrrolylmethane (IIIh'') and also a small amount of the ether (IVa) were also found among the reaction products. Table 5 gives the conditions for the reaction of the investigated

five-membered heterocycles with the alcohol (IIa) in the presence of the cation exchanger (1), under which the largest yields of the 2-furyl(heteroaryl)methanes (III) were obtained.

In simplicity and in the yields, the obtained results are better than the few known methods for the synthesis of furylmethane derivatives (III). (Potential regions of application are extremely varied [2, 52, 53].) Thus, furyl(thienyl)methane (IIIg) was obtained earlier [54] with a yield of 45-53% by the metallation of thiophene with butyllithium followed by alkylation with 2-chloromethylfuran. The pyrrole derivative (IIIh') was synthesized by the reduction of 2-furyl 2-pyrrolyl ketone with lithium aluminum hydride or sodium borohydride (yields 40 and 75% respectively) [53, 55]. [Published data [1, 3] on the synthesis of the furan derivative (IIIa) were given above.]

In the reaction of alcohol (IIa) with thiophene, the ether (IVa) was also obtained in addition to the methane derivative (IIIg). This compound is hardly formed at all during the alkylation of furan, and in the case of pyrrole its yield is small.

Additional experiments showed that the ether (IVa) is not formed during contact between the alcohol (IIa) and the cation exchanger (1). However, the ether (IVa) is formed in the reaction of the previously obtained individual compound (IIIg) with the alcohol (IIa) in the presence of the cation exchanger (1). It can therefore be supposed that, by blocking or modifying a certain part of the centers of the cation exchanger, the diheteroarylmethane (IIIg) promotes intermolecular dehydration of the alcohol (IIa), leading to the ether (IVa). The fact that there are H<sup>+</sup> centers with different strengths and accessibility in the sulfo cation exchangers is demonstrated by investigations carried out recently [28]. Analogous processes evidently also occur in the case of the alkylation of pyrrole but to a lesser degree. The proposed scheme for the formation of the main products from the alkylation of furan, thiophene, and pyrrole by the alcohol (IIa) in the presence of the cation exchanger (1) is given below.

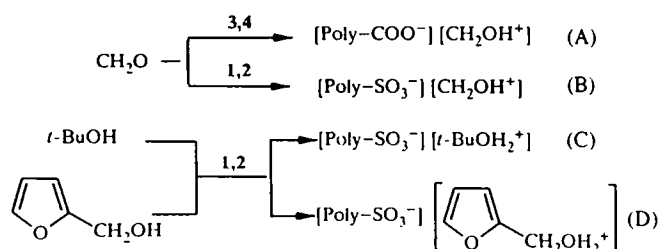


The data on the regio-orientation of the alkylation of furan, thiophene, and pyrrole by furfuryl and *tert*-butyl alcohols in the presence of the cation exchanger (1) (Table 6) indicate that the alkylation of furan and thiophene by the alcohol (IIa) takes place regiospecifically at position 2 of these heterocycles, while pyrrole is also alkylated to a small degree at position 3. During alkylation by *tert*-butyl alcohol, substitution is more characteristic for pyrrole than for the other heterocycles. In the case of thiophene, a mixture of 2- and 3-(*tert*-butyl)thiophenes is formed, but in all cases alkylation at the  $\alpha$  position of the heterocycles predominates.

## 5. CONCLUSION

The investigations into the hydroxymethylation and alkylation of heterocyclic compounds at cation exchangers made it possible to obtain a series of valuable substances and also to reveal certain relationships governing these acid-catalyzed reactions.

Strongly acidic cation exchangers protonate formaldehyde and also certain alcohols (*tert*-butyl, furfuryl), forming a carbocation, where the counterion is the polymeric anion. Weakly acidic cation exchangers protonate formaldehyde but do not protonate the investigated alcohols. The further progress of the reactions and their main directions depend on the substrate with which the ion pairs react.



The ion pair A does not react with furan (or with the methane derivatives of thiophene and pyrrole), but in reaction with sylvane and furfuryl alcohol it gives the corresponding alcohols, i.e., 5-methylfurfuryl alcohol and 2,5-dihydroxymethylfuran. Pair B (unlike A) reacts with furan and 2,5-dimethylfuran to form the corresponding alcohols, but with 2-methylfuran and 2-methylthiophene it gives the corresponding methane derivatives. The methane derivatives are also formed in the reaction of the pair D with furan, thiophene, and pyrrole. The reaction of these heterocycles and also of N-methylpyrrole with pair C leads to the *tert*-butylation of furan at positions 2 and 5 of the ring and of thiophene and pyrrole at positions 2 and 3.

Thus, it is seen that the directions of acid-catalyzed hydroxymethylation with formaldehyde and alkylation with alcohols depend on all three components of the processes, i.e., the substrate, the alkylating agent, and the employed H<sup>+</sup> cation exchanger.

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