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SYNTHESIS OF 4-METHYL-2,3,4-TRICHLOROTETRAHYDROPYRAN AND SEVERAL FEATURES OF THE STEREOCHEMISTRY OF THE NUCLEOPHILIC SUBSTITUTION OF THE α-CHLORINE ATOM

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A convenient method has been developed for the synthesis of 4-methyl-2,3,4-trichlorotetrahydropyran by the chlorination of 4-methyl-4-chlorotetrahydropyran, 4-methyl-5,6-dihydro-2H-pyran and its dichloride. A study was carried out on the reactions of 4-methyl-2,3,4-trichlorotetrahydropyran with alcohols, with sodium thiocyanate and Grignard reagents. PMR spectroscopy was used to study the stereochemistry of 4-methyl-2,3,4-trichlorotetrahydropyran and its derivatives, 2-substituted 4-methyl-3,4-dichlorotetrahydropyrans. The dechlorination of these dichloro derivatives by metallic sodium leads to 2,4-disubstituted 5,6-dihydro-2H-pyrans with high regioselectivity.

In recent years, 4-methyl-5,6-dihydropyran and 4-methyltetrahydropyran have become objects of intensive study [1-7] since, as industrial waste products, they are model molecules of a large series of di- and tetrahydropyrans obtained from available petrochemical raw materials [8, 9].

This led to the development of methods for the synthesis of citric acid [4], dehydromevalolactone [6], and various isoprenoid synthones [10].

In the course of these studies, we have found that the chlorination of 4-methyl-5,6-dihydro-2H-pyran gives trichloride I (43%) containing an extremely active chlorine atom toward amines. Trichloride I was also obtained in the chlorination of the hydrochloride of 4-methyl-5,6-dihydro-2H-pyran and 4-methylenetetrahydropyran (4-methyl-4-chlorotetrahydropyran (62%) [7]) and the dichloride of 4-methyl-5,6-dihydro-2H-yran (4-methyl-3,4-dichlorotetrahydropyran (66%). On the basis of the results of the chlorination of THF [11], we may assume that the chlorination of 4-methyl-4-chlorotetrahydropyran proceeds through the α-chlorination of the tetrahydropyran, dehydrochlorination of the intermediate α-chloroether to a dihydropyran and the subsequent chlorine addition to this dihydropyran to give trichloride I. (Formula, top, following page.)

PMR spectroscopy showed that the reaction gives a 4:1 mixture of isomeric trichlorides (the methyl peaks were taken as diagnostic) with predominance of the isomer with the downfield

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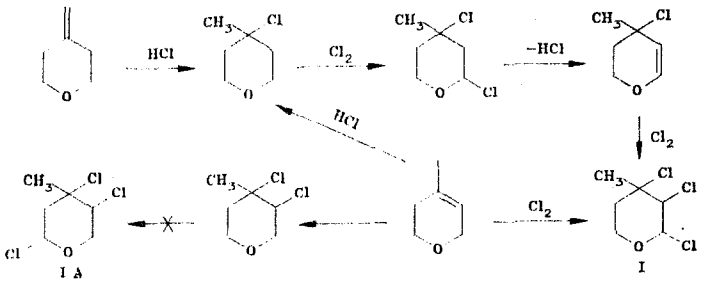
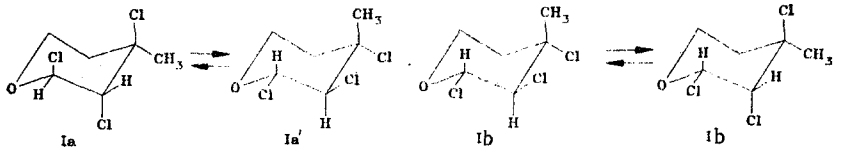
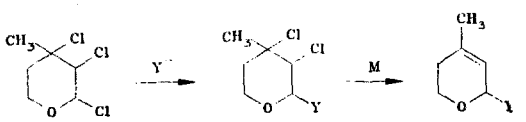


methyl group signal. In addition, a double resonance study reliably established that the two vicinal methine protons in the PMR spectrum appear with a coupling constant of 3.2 Hz. These data and the finding that the vicinal diaxial proton coupling is 6-10 Hz [12] permits us to exclude the structure of 4-methyl-2,4,5-trichlorotetrahydropyran (IA) in favor of 4-methyl-2,3,4-trichlorotetrahydropyran (I) and give preference for structures Ia and Ib. Since the minor component has an upfield methyl group and the conformational energy of chlorine is markedly less than for the methyl group [13], isomer Ia must predominate in this mixture. Indeed, comparison of the PMR spectra of model compounds, specifically, cis- and trans-3,4-dihydroxy-4-methyltetrahydropyrans and their acetates [14] indicates that the equatorial methyl group of the cis-isomer is a lower field than this group in the trans-isomer.



Confirmation of the structure of the trichlorides was found in a study of the chemical properties of I. Trichloride I reacts readily with Grignard reagents, alcohols and sodium thiocyanate to form 2-alkyl- (or 2-aryl-), 2-alkoxy-, or 2-thiocyanato-4-methyl-3,4-dichlorotetrahydropyrans II in high yields (Table 1). Products II under dechlorination upon reaction with metals to form 2-substituted 5,6-dihydro-2H-pyrans identical (in the case of the alkyl derivatives) to samples obtained in our previous work [15].

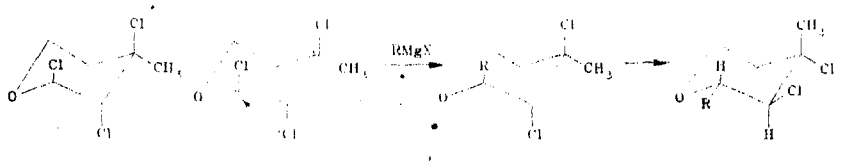
In addition to the proof of structure of trichloride I, this pathway for the preparation of dihydropyrans is a very general and highly regioselective (>99%) method for the formation of 2-substituted 5,6-dihydro-2H-pyrans (Table 2).



II a $Y=C_4H_9$, b $Y=i\text{-}C_5H_{11}$, c $Y=C_6H_5$, d $Y=CH_2=CH-CH_2$, e $Y=OCH_3$, f $Y=i\text{-}C_3H_7O$, g $Y=i\text{-}C_5H_{11}O$, h Y=SCN; M=Na, Zn

A study of the reaction of trichloride I with Grignard reagents revealed a very interesting effect, namely, there is apparent retention of the configuration at the α-carbon atom instead of the expected inversion at the reaction site as found for derivatives of cyclohexane [16] and glucosyl halides [17], i.e., instead of local inversion at the reaction site, the substitution is accompanied by complete inversion of the heterocycle analogous to that proposed in the reaction of 2,3-dichlorotetrahydropyran with Grignard reagents [18]. The same conclusion was drawn by comparing the integral intensities of the low and high field methyl group signals of starting trichloride I and the products of its reactions with nucleophiles. Indeed, if the substitution of the axial α-chlorine atom by a nucleophile (studied in greatest detail for C_6H_5MgX) occurred with local inversion, it would lead to a 2e-alkyl (or 2e-aryl) derivative of II and, in the final analysis, to strengthening of the conformer with a 4e-methyl group. However, the coupling constant of the vicinal methine protons in the PMR spectrum of the compound obtained is 9.5 Hz. This value indicates that, in contrast to expectation, the nucleophile apparently attacks for the same side from which the nucleophilic group leaves. In our opinion, this is a consequence of an intramolecular reaction of the p electrons of the β-chlorine atom with the reaction site leading to prevention of the direct attack of

the nucleophile at the α-C—Cl bond prior to the substitution. Then, the newly formed 2a-aryl (or 2a-alkyl) group which has much higher steric requirements than the same substituents in other positions of the tetrahydropyran ring [17] (inverse anomeric effect) causes the complete inversion of the heterocycle.



The reaction with isomer Ib proceeds analogously.

This explanation is not in accord with the data given above for the substitution of glucosy halides, which indicate that a β-atom with p electrons such as oxygen is incapable of retaining the configuration of the reaction site carbon atom. However, this contradiction is only apparent. Oxygen and chlorine atoms behave differently as neighboring groups with p electrons. Oxygen, which is one of the best p electron donors for the closure of five- and six-membered rings, is completely inert in 1,3-interactions. On the other hand, chlorine atoms may rather effectively act as p electron donors in 1,3-interactions [19].

The reaction of the trichloride with alcohols is also interesting. A mixture of two isomeric ethers is formed. These products differ both in the chemical shift of the 4-methyl group protons and the coupling constants of the 2-H and 3-H vicinal atoms (2-4 and 6-10 Hz). This apparently indicates the formation of isomer II with 2-,3-diaxial hydrogen atoms, i.e., the replacement is again accompanied (although to a reduced extent) by inversion of entire ring. However, we should note that while such inversion is entirely reasonable for derivatives of II with 2a-alkyl and 2a-aryl substituents which display an inverse anomeric effect, it is far from obvious for the 2a-alkoxy group with an anomeric effect. Hence, we considered data obtained for the series of 6-methyl-1,3-dioxanes with 4-fluorinated methyl groups. The trifluoromethyl group in these molecules occupies an axial position due to the anomeric effect. The same preference is found (although to a reduced extent) for the difluoromethyl group, while the fluoromethyl group has equatorial orientation. The dipole—dipole interaction (anomeric effect) presumably decreases in this series of fluoro derivatives and in the fluoromethyl derivative, this interaction is insufficient for the suppression of steric hindrance [20].

It would appear that this behavior is analogous to that found in the series of alkoxy derivatives II. The substitution initially proceeds as described above for Grignard reagents and leads to the formation of isomers with 2a-alkoxy groups. Thus, since the conformational energy of the anomeric effect of the alkoxy groups is significantly less than these values for halogen atoms (for example, these values are 2.65 and 1.5 kcal/mole for the chlorine atom and methoxy group, respectively). The effect of steric factors begins to become significant. Indeed, we have noted that the fraction of the isomer with 2,3-diaxial hydrogen atoms increases with increasing bulk of the alkyl group of the alcohol used. Thus, the isomer ratio is 1:1 in the case of methanol, 1:3 in the case of 2-propanol and 1:4 in the case of isopentyl alcohol.

EXPERIMENTAL

The gas-liquid chromatographic analysis was carried out on an LKhM-80-1 chromatograph using a katharometer detector, 40-60 ml/min helium gas flow rate, and a 2000 × 3 mm steel column packed with 15% Apiezon L on Chromaton NAW (0.20-0.25 mm) and a 3000 × 3 mm steel column packed with 15% PEGA on Chromaton NAW (0.20-0.25 mm). The separation temperature was 100-150°C. The PMR spectra were taken on a Perkin—Elmer R-12B spectrometer at 60 MHz and on a Tesla BS-497 spectrometer at 100 MHz in CCl_4 and $CDCl_3$ with HMDS as the internal standard.

4-Methyl-2,3,4-trichlorotetrahydropyran (I). A. A chlorine stream was passed with stirring through 26.9 g (0.2 mole) 4-methyl-4-chlorotetrahydropyran at 35-40°C for 4 h. Distillation in vacuum gave 25.2 g (62%) trichloride I with bp 97-100°C (3 mm), n_D^{20} 1.5145, d_4^{20} 1.3917. PMR spectrum ($CDCl_3$): 6.06 (1H, d, J = 3.2 Hz, OCHCl), 4.26 (1H, d, J = 3.2 Hz, CHCl), 3.94 (2H, m, CH_2O), 2.21 (2H, m, CH_2), 1.82 ppm (3H, s, CH_3). Found: C, 35.2; H, 4.6; Cl 51.9%. Calculated for $C_6H_9Cl_3O$: C 35.4; H 4.4; Cl 52.3%.

B. An analogous procedure gave 17.2 g (43%) trichloride I from 19.6 g (0.2 mole) 4-methyl-5,6-dihydro-2H-pyran.

TABLE 1. Some Characteristics of IIa-g

Compound	bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	PMR spectrum, δ, ppm	Found, %			Chemical formula	Calculated, %			Yield, %
					C	H	Cl		C	H	Cl	
IIa	98—100 (3)	1,4825	1,1096	4,13 (1H, m, CHCl), 3,72 (3H, m, OCH_2, OCH), 2,02 (2H, m, CH_2), 1,69 (3H, s CH_3), 1,32 (6H m, CH_2), 0,88 (3H, т, J=5,3 Hz, CH_3)	53,0	8,1	31,0	$C_{10}H_{18}Cl_2O$	53,3	8,0	31,5	51
IIb	102—105 (3)	1,4812	1,0968	4,15 (1H, m, CHCl), 3,72 (3H, m, OCH_2 and OCH), 2,19 (2H, t, J=5,3 Hz, CH_2), 1,68 (3H, s, CH_3), 1,32 (5H, m, CH_2, CH), 0,83 [6H, d, J=5,3 Hz $CH(CH_3)_2$]	55,3	8,2	29,3	$C_{11}H_{20}Cl_2O$	55,2	8,4	29,7	59
IIc	152—156 (3)	1,5558	1,2402	7,51 (5H, s, C_6H_5), 4,28 (2H, AB, J_{AB}=9,5 Hz, C_6H_5CH and CHCl), 3,63 (2H, m, OCH_2), 2,25 (2H, m, CH_2), 1,97 (3H, s, CH_3)	58,3	5,3	29,1	$C_{12}H_{14}Cl_2O$	58,8	5,6	29,0	60
IId	74—76 (2)	1,4960	1,1601	5,75 (1H, m, CH=C), 5,03 (2H, m, $C=CH_2$), 4,13 (1H, m, CHCl), 3,71 (3H, m, OCH_2 and OCH), 2,28 (4H, m, CH_2), 1,68 (3H, s, CH_3)	51,5	6,5	33,6	$C_9H_{14}Cl_2O$	51,7	6,7	34,0	59
IIe	64—67 (3)	1,4860	1,2540	5,05 and 4,59 (1H, d, J=2,5 and J=6,7 Hz e- and a-CHO), 4,23 and 4,11 (1H, d, J=2,5 and J=6,7 Hz e- and a-CHCl), 3,83 (2H, m, OCH_2), 3,59 (3H, s, OCH_3), 2,23 (2H, m, CH_2), 1,93 and 1,84 (3H, s, CH_3)	42,0	6,2	35,4	$C_7H_{12}Cl_2O_2$	42,2	6,0	35,7	62
IIf	70—72 (3)	1,4775	1,1772	4,89 and 4,39 (1H, d, J=3,3 и J=6,7 Hz e- and a-CHO), 3,92 (1H, m, CHCl), 3,62 (3H, m, OCH_2, OCH), 2,12 (2H, m, CH_2), 1,71 и 1,62 (3H, s, CH_3), 1,16 and 1,07 [6H, d, J=2,6Hz, $CH(CH_3)_2$]	47,3	7,2	31,0	$C_9H_{16}Cl_2O_2$	47,6	7,0	31,3	61
IIg	93—95 (3)	1,4810	1,1342	4,83 and 4,41 (1H, d, J=2,6 and J=6,6 Hz, e- and a-CHO), 3,97 (1H, m, CHCl), 3,38 (4H, m, OCH_2), 2,11 (2H, m, CH_2), 1,73 and 1,66 (3H, s, CH_3), 0,88 [6H, d, J=6,6 Hz, $CH(CH_3)_2$]	51,4	8,0	27,7	$C_{11}H_{20}Cl_2O_2$	51,8	7,8	27,8	65

TABLE 2. Some Characteristics of IIIa-g

Compound	bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	PMR spectrum, δ, ppm	Found, %		Chemical formula	Calculated, %		Yield, %
					C	H		C	H	
IIIa	73—75 (11)	1,4556	0,8794	5,21 (1H, m, =CH), 3,42 (3H, m, OCH_2 and OCH), 2,16 (2H, m, CH_2), 1,66 (9H, m, CH_2, $=C-CH_3$), 0,99 (3H, dist. t, CH_3)	77,8	11,5	$C_{10}H_{18}O$	77,9	11,7	78
IIIb	81—83 (13)	1,4505	0,8639	5,25 (1H, m, =CH), 3,52 (3H, m, OCH_2 and OCH), 2,03 (2H, m, CH_2), 1,45 (8H, m CH_2, $=C-CH_3$), 0,83 [6H, d, J=6 Hz, $CH(CH_3)_2$]	78,3	11,6	$C_{11}H_{20}O$	78,6	11,9	79
IIIc	100—103 (2)	1,5505	0,9080	7,19 (5H, s, C_6H_5), 5,42 (1H, m, CHC_6H_5), 4,93 (1H, m =CH), 3,72 (2H, m, OCH_2), 2,11 (2H, m CH_2), 1,68 (3H, br $=C-CH_3$)	82,6	8,2	$C_{12}H_{14}O$	82,7	8,0	80
III d	62—63 (12)	1,4675	0,8691	5,51 (4H, m, =CH, $CH=CH_2$), 3,72 (3H, m, OCH_2, OCH), 2,18 (4H, t, J=6,9 Hz, CH_2), 1,68 (3H, br, $=C-CH_3$)	78,3	10,2	$C_9H_{14}O$	78,3	10,1	75
III e	50—52 (12)	1,4555	0,9989	5,35 (1H, m, CHO), 4,78 (1H, m, =CH), 3,66 (2H, m OCH_2), 3,28 (3H, s, OCH_3), 2,11 (2H, m CH_2), 1,65 (3H, br, $=C-CH_3$)	65,5	9,3	$C_7H_{12}O_2$	65,6	9,4	74
III f	62—64 (12)	1,4540	0,9631	5,35 (1H, m, CHO), 4,78 (1H, m, =CH), 3,66 (3H, m, OCH_2 and OCH), 2,11 (2H, m, CH_2), 1,68 (3H, br, $=C-CH_3$), 1,15 and 1,05 [6H, d, J= =3,3 Hz, $CH(CH_3)_2$]	69,1	10,0	$C_9H_{16}O_2$	69,2	10,2	76
III g	82—83 (13)	1,4525	0,8874	5,35 (1H, m, CHO), 4,78 (1H, m, =CH), 3,59 (4H, m, CH_2O), 2,11 (2H, m, CH_2), 1,69 (3H, br, $=C-CH_3$), 0,87 [6H, d, J=6 Hz, $CH(CH_3)_2$]	71,6	10,7	$C_{11}H_{20}O_2$	71,7	10,9	81

C. Similarly, 26.8 g (66%) trichloride I was obtained from 26.7 g (0.2 mole) 4-methyl-3,4-dichlorotetrahydropyran.

3,4-Dichloro-4-methyltetrahydropyran. A stream of 7.8 g (0.11 mole) chlorine was passed through a mixture of 9.8 g (0.1 mole) 4-methyl-5,6-dihydro-2H-pyran in 50 ml ethyl acetate at from −65 to −70°C. The reaction mixture was brought to room temperature. Ethyl acetate was distilled off and vacuum distillation gave 9.2 g (54%) of a compound with bp 85-87°C (11 mm), n_D^{20} 1.4940, d_4^{20} 1.2609. PMR spectrum (CCl_4): 4.28 (1H, t, J = 2.7 Hz, CHCl), 4.18 (2H, m, OCH_2), 3.72 (2H, m, OCH_2), 2.05 (2H, m, CH_2), 1.68 ppm (3H, s, CH_3). Found: C, 42.2; H, 5.8; Cl, 42.3%. Calculated for $C_6H_{10}Cl_2O$: C, 42.6; H 5.9; Cl, 42.0%.

2-Alkyl-(or2-Aryl-)3,4-dichloro-4-methyltetrahydropyran (IIa-d). A sample of 10.2 g (0.05 mole) trichloride I was added to the Grignard reagent obtained from 2.4 g (0.1 mole) magnesium and 0.1 mole halide in 100 ml absolute ether at 0°C. The reaction mixture was then heated for 1 h at 32°C, cooled to 0°C and decomposed with saturated aqueous ammonium chloride. The reaction mixture was left for an additional 3 h. The ethereal solution was decanted from the precipitate and distilled in vacuum (Table 1).

2-Alkoxy-3,4-dichloro-4-methyltetrahydropyran (IIe-g). A sample of 0.055 mole trichloride I was added to a mixture of 30 ml alcohol and 0.1 mole potassium carbonate at 50°C. The mixtur was heated at this temperature for 6 h and then treated with water and extracted with ether. The ethereal extracts were combined, dried over $CaCl_2$ and distilled (Table 1).

3,4-Dichloro-4-methyl-2-thiocyanatotetrahydropyran (IIh). A sample of 10.2 g (0.05 mole) trichloride I was added to a mixture of 4.8 g (0.06 mole) sodium thiocyanate and 25 ml DMF at 25°C. The mixture was brought to 40°C and stirred for 4 h. DMF was distilled off and the reaction mass was washed with water and extracted with ether. The ethereal extract was dried over $CaCl_2$. Ether was removed and distillation gave 4.6 g (41%) of a compound with bp 112-114°C (3 mm), n_D^{20} 1.5440, d_4^{20} 1.3787. PMR spectrum (CCl_4): 5.62 and 5.25 (1H, d, J = 2.7 and J = 8.7 Hz, e- and α-CHSCN), 4.02 (3H, m, CHCl and OCH_2), 1.82 and 1.71 ppm (3H, s, CH_3). Found: C, 37.4; H 4.1; Cl, 31.1; N, 6.4; S, 13.9%. Calculated for $C_7H_9Cl_2NOS$: C, 37.2; H, 4.0; Cl, 31.4; N, 6.2; S, 14.1%.

2-Substituted 4-Methyl-5,6-dihydro-2H-pyran (IIIa-g). A sample of 0.1 mole dichloride IIa-g) was added to a flask containing 0.25 mole metallic sodium in 100 ml absoluted ether. The reaction mixture was stirred at 32°C for 15-20 h and then washed with water, extracted with ether. The ethereal extracts were combined, dried over $MgSO_4$ and distilled (Table 2).

B. Under analogous conditions, 0.25 mole zinc and 0.1 mole dichloride II gave dihydropyran IIIa-g. Gas-liquid chromatography indicated the formation of 3-10% isomeric 2-substituted 4-methyl-3,6-dihydro-2H-pyran.

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STRUCTURE OF THE PRODUCTS OF THE O-MONOALKYLATION OF PYROCATECHOL BY α-BROMOKETONES

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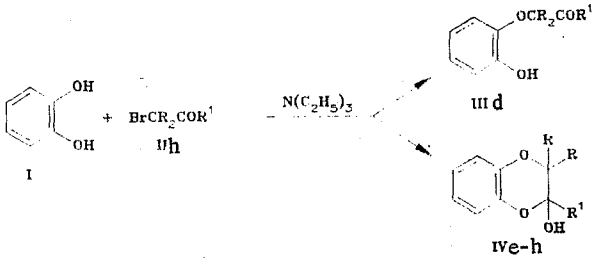
The reaction of pyrocatechol with α-bromoketones in the presence of triethylamine leads to the formation of o-hydroxyphenoxymethyl ketones or 2-hydroxy-2,3-dihydro-1,4-benzodioxines. PMR spectroscopy revealed ring–chain tautomerism of the products obtained. The relative effect of structural factors on the stability of the ring structure was evaluated.

The products of the monoalkylation of pyrocatechol I by chloroacetone [1] and phenyacyl bromide (2) were initially considered to be phenols III. Later spectroscopic studies showed that both these compounds have cyclic structure IV, while their sodium derivatives exist as the open form III [3, 4]. There have also been reports of the preparation of the acyclic structural analog of III (R = H, R^1 = $COCH_3$) and its cyclic derivatives IV [R^1 = $C(OCH_3)_2CH_3$ and $C(OCH_2)CH_3$] by an independent method [5, 6]. No data have been given for the ketol–lactol equilibrium of these compounds in solution. It was of interest to determine the preparative range of this reaction in order to elucidate the capacity of its products to under ring–chain transformations and establish the relationship of this capacity to the structure of these compounds.

The reaction was carried out with a twofold excess of diphenol I relative to the alkylating component. Triethylamine was used as the base instead of the alkaline reagents previously employed. These conditions permitted us to suppress side reactions such as 0,0'-dialkylation, oxidation, Favorskii rearrangement and dehydrobromination, simplify the synthesis procedure and enhance the yield of the O-monoalkylation product. The reaction is rather general in nature, encompassing α-bromo derivatives of aromatic, heteroaromatic and aliphatic ketones with both normal and branched hydrocarbon chains IIa-h. The structure of the starting alkylation agent has only a slight effect on the yield but determines the cyclic or acyclic structure of the final product. Thus, the reaction with bromoketones IIa-d leads to the formation of o-hydroxyphenoxymethyl ketones IIIa-d. The other bromoketones gave 2-hydroxy-2,3-dihydro-1,4-benzodioxines IVe-h.



IIa–g, IIIa–d, IVe–g R=H, IIh, IVh R=CH_3; II, IIIa R^1=2,4,6-$(CH_3)_3C_6H_2$, b R^1=2-thienyl, c R^1=2-furyl, d R^1=2,4,5-$(CH_3)_3C_6H_2$; II, IVe R^1=C_6H_5, f R^1=t-C_4H_9, g,h R^1=CH_3

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