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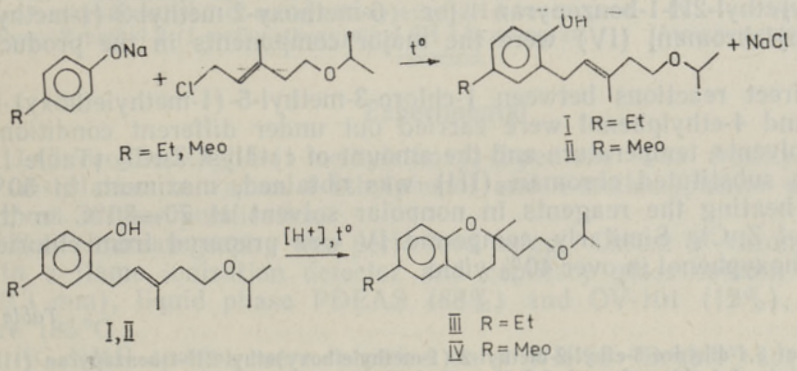
SYNTHESIS OF SUBSTITUTED CHROMANS FROM 4-ETHYLPHENOL, 4-METHOXYPHENOL AND 1-CHLORO-3-METHYL-5-(1-METHYLETHOXY)-2-PENTENE

Synthesis of 3,4-dihydro-2H-1-benzopyran (chroman) derivatives has drawn considerable attention [1]. Many of these compounds are biologically active, having mostly potential vitamin E activity, but e. g. 6,7-dimethoxy-2,2-dimethylchroman has been investigated for its insecticidal properties [2].

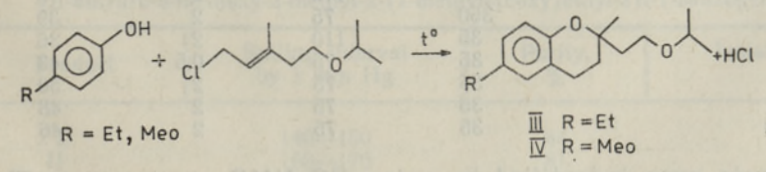
With a view to obtain new potential biologically active compounds, we have investigated the synthesis of chroman derivatives, starting from 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene and *p*-substituted phenols, such as 4-ethylphenol and 4-methoxyphenol.

It would be possible to obtain *o*-allylic phenols (in our case (I) and (II)) by C-alkylation of phenols alkali metal salts with chloride. The cyclization of 3′-substituted allylic phenols by Claisen presumably gives the corresponding chroman derivatives (III) and (IV).



For example, synthesis of 6-methoxy-2-[(3-methyl)-2-butenyl]phenol from alkali metal salt of 4-methoxyphenol and 1-bromo-3-methyl-2-butene and further preparation of 6-methoxy-2,2-dimethylchroman by acid-catalyzed cyclization of allylic phenol has been described in [3].

The direct reaction between allylic chloride and phenol in the absence of alkali would be also possible.



Similarly, 3,4-dihydro-2,2,5,7,8-pentamethyl-2H-1-benzopyran-6-ol has been obtained by heating 2,3,5-trimethyl-1,4-benzenediol with 1-bromo-3-methyl-2-butene [4].

In this work we have investigated the possibility of synthesizing substituted chromans (III) and (IV) using both ways described.

Results and discussion

1-Chloro-3-methyl-5-(1-methylethoxy)-2-pentene (a mixture of isomers with an *E*:*Z* ratio approximately 3:1) was prepared by telomerization of 2-(chloromethoxy)propane with 2-methyl-1,3-butadiene [5]. The sodium salts of 4-ethylphenol and 4-methoxyphenol were prepared by reacting these phenols with NaOH in toluene. The suspension prepared was dried by removal of a water-toluene azeotropic mixture. Results of further alkylation showed that yields of phenol salts prepared this way have been good. Thus, although for preparation of dry 4-methoxyphenol sodium salt e. g. sodium hydride is recommended to use [3], we have succeeded in it, using more conventional reagents and methods.

The reaction of phenol salts with chloride was carried out by heating their mixture in toluene at 60—80 °C. The products obtained were purified by distillation. Gas chromatography and ^{13}C NMR analysis showed that the major components were, according to the starting phenol, 6-ethyl-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (I) and 6-methoxy-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (II). Both the allylic phenols obtained were the mixtures of *E* and *Z* isomers with the same ratio of *E*:*Z* as the chloride reagent.

The cyclization of allylic phenols (I) and (II) was carried out by the known method [3], heating them in acetic acid in the presence of HCl. As it was theoretically assumed, the corresponding 3,4-dihydro-6-ethyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran [or 6-ethyl-2-methyl-2-(1-methylethoxy)ethylchroman] (III) and 3,4-dihydro-6-methoxy-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran [or 6-methoxy-2-methyl-2-(1-methylethoxy)ethylchroman] (IV) were the major components in the products obtained.

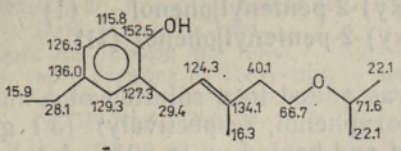
The direct reactions between 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene and 4-ethylphenol were carried out under different conditions, varying solvents, temperature and the amount of catalyst $ZnCl_2$ (Table 1). Again the substituted chroman (III) was obtained, maximum in 50% yield, by heating the reagents in nonpolar solvent at 70—80 °C in the presence of $ZnCl_2$. Similarly, compound IV was prepared from chloride and 4-methoxyphenol in over 40% yield.

Table 1

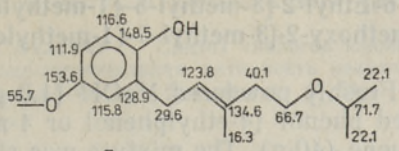
Preparation of 3,4-dihydro-6-ethyl-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran (III) by reaction of 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene with 4-ethylphenol

Solvent	Molar relation Phenol/$ZnCl_2$	T, °C	Time, h	Yield, %
—	—	100	2	24
Toluene	—	110	3	16
Toluene	350	75	2	39
Toluene	35	110	2	36
Toluene	35	75	0.5	43
Toluene	35	75	2	50
Benzene	35	75	2	48
Light petroleum	35	75	2	46

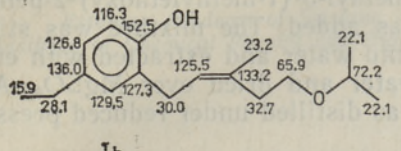
The products were indentified by using ^{13}C NMR spectroscopy. The chemical shifts for compounds (I)—(IV) were assigned (the Figure) on the basis of peak intensities, chemical shifts of model compounds (ethylbenzene, methoxybenzene, 2-allylphenol [6], N-(3-methyl-5-isopropoxy)-2-penthenylbenzylamine [7]) and using the information obtained from mono-resonance spectra.



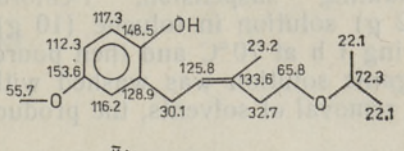
Ia



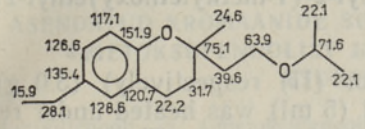
IIa



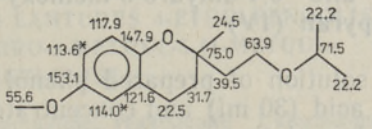
Ib



IIb



III



IV

^{13}C chemical schifts in ppm downfielded from internal Me_4Si: Ia — 6-ethyl-2-[3-methyl-5-(1-methylethoxy)-2(*E*)-pentenyl]phenol, Ib — 6-ethyl-2-[3-methyl-5-(1-methylethoxy)-2(*Z*)-pentenyl]phenol, IIa — 6-methoxy-2-[3-methyl-5-(1-methylethoxy)-2(*E*)-pentenyl]phenol, IIb — 6-methoxy-2-[3-methyl-5-(1-methylethoxy)-2(Z)-pentenyl]phenol, III — 3,4-dihydro-6-ethyl-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran, IV — 3,4-dihydro-6-methoxy-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran. * Assignements may be reversed.

Experimental

1-Chloro-3-methyl-5-(1-methylethoxy)-2-pentene was freshly purified by distillation in vacuo. 4-Ethylphenol and 4-methoxyphenol were used without further purification.

Gas chromatography was performed using "Chrom 5" chromatograph with a flame ionization detector and capillary glass column (47000××0.3 mm), liquid phase PDEAS (88%) and OV-101 (12%), temperature 185°C.

^{13}C NMR spectra were recorded on a WH-90 "Bruker" spectrometer (22.62 MHz) in $CDCl_3$ solution, using tetramethylsilane as an internal standard.

Properties and yields of products are given in Table 2.

Table 2

Properties and yields of products: 4-ethyl-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (I), 4-methoxy-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (II), 3,4-dihydro-6-ethyl-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran (III) and 3,4-dihydro-6-methoxy-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran (IV)

Product	Boiling interval by 1 mm Hg	Purity, %	Isolated yield, %
I	140—150	84	70
II	160—170	81	55
III a)*	120—130	89	54 (38**)
b)*	120—130	96	50
IV a)*	130—140	87	47 (26**)
b)*	130—140	95	44

* Method of obtaining, described in experimental.
** Summary yield of a two-step process.

6-Ethyl-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (I) and 6-methoxy-2-[3-methyl-5-(1-methylethoxy)-2-pentenyl]phenol (II)

Freshly powdered NaOH (1.0 g) was added to a solution of a substituted phenol (4-ethylphenol or 4-methoxyphenol, respectively) (3.1 g) in toluene (40 g). The mixture was stirred and heated up to 80°C. A toluene-water mixture (~20 ml) was removed under reduced pressure. To the remaining suspension, 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene (4.2 g) solution in toluene (10 g) was added. The mixture was stirred during 1 h at 70°C and then poured into water and extracted with ether. Organic solution was washed with water and dried over $MgSO_4$. After the removal of solvents, the product was distilled under reduced pressure.

3,4-Dihydro-6-ethyl-2-methyl-2-(1-methylethoxy)ethyl-2H-1-benzopyran (III) and 3,4-dihydro-6-methoxy-2-methyl-2-(1-methylethoxy)ethyl-2H-1-penzopyran (IV)

a) A solution of prepared phenol ((I) or (II) respectively) (3.0 g) in acetic acid (30 ml) and concentrated HCl (5 ml) was heated under reflux for 1 h and then evaporated under reduced pressure. The residue was cooled and extracted with ether. After washing with 10% aqueous KOH and water the solution was dried over $MgSO_4$. After drying ether was evaporated and the product distilled.
b) A solution of *p*-substituted phenol (4-ethylphenol or 4-methylphenol respectively) (3.1 g) and 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene (4.2 g) in toluene (25 ml) was stirred in the presence of $ZnCl_2$ (0.1 g) for 2 h of 75°C. The product was isolated as described above.

Conclusions

By C-alkylation of 4-ethyl- and 4-methoxyphenol sodium salts with 1-chloro-3-methyl-5-(1-methylethoxy)-2-pentene corresponding *o*-allylic phenols were obtained. Further cyclization of those gave the corresponding substituted 3,4-dihydro-2H-1-benzopyrans (chromans). The latter were also obtained by direct reaction of starting phenols with chloride (in the presence of $ZnCl_2$).

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ASENDATUD KROMAANIDE SÜNTEES LÄHTUDES 4-ETÜÜLFENOOLIST, 4-METOKSÜFENOOLIST JA 1-KLORO-3-METÜÜL-5-(1-METÜÜLETOKSÜ)-2-PENTEENIST

4-etüülfenooli ja 4-metoksüfenooli Na-fenolaatide reaktsioonil 1-kloro-3-metüül-5-(1-metüületoksü)-2-penteeniga tolueenis on saadud vastavad *o*-alkenüülfenoolid ning viimaste tsükliseerimisel vastavalt 3,4-dihüdro-6-etüül-2-metüül-2-(1-metüületoksü)etüül-2H-1-bensopüraan ja 3,4-dihüdro-6-metoksü-2-metüül-2-(1-metüületoksü)etüül-2H-1-bensopüraan. Samad ühendid on saadud ka otse lähtefenoolide ja kloriidi reaktsioonil (kuumutamisel mittepolaarses lahustis $ZnCl_2$ manulusel saagisega üle 40%). On määratud sünteesitud ainete ^{13}C-tuumade keemilised nihked.

Антс МААСАЛУ, Аарe ЛАХТ, Койт ЛЭЭТС

СИНТЕЗ ЗАМЕЩЕННЫХ ХРОМАНОВ ИЗ 4-ЭТИЛФЕНОЛА, 4-МЕТОКСИФЕНОЛА И 1-ХЛОР-3-МЕТИЛ-5-(1-МЕТИЛЭТОКСИ)-2-ПЕНТЕНА

Реакцией Na-фенолятов 4-этил- и 4-метоксифенола с 1-хлор-3-метил-5-(1-метилэтокси)-2-пентеном в толуоле получены соответствующие *о*-алкенилфенолы, а циклизацией последних — 3,4-дигидро-6-этил-2-метил-2-(1-метилэтокси)этил-2H-1-бензопиран и 3,4-дигидро-6-метокси-2-метил-2-(1-метилэтокси)этил-2H-1-бензопиран. Эти замещенные хроманы получены и прямой реакцией исходных фенолов и хлорида при нагревании в неполярном растворителе (в присутствии $ZnCl_2$) с выходами до 50%. Определены химические сдвиги ядер ^{13}C синтезированных соединений.