SYNTHESIS OF o- AND p-HYDROXYACETOPHENONES AND 2-METHYL-4,6-DIARYLPYRYLIUM AND 2-ARYL-4-METHYLBENZOPYRYLIUM SALTS BY ACETYLATION OF SOME PHENOLS

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UDC 547.577.814.5

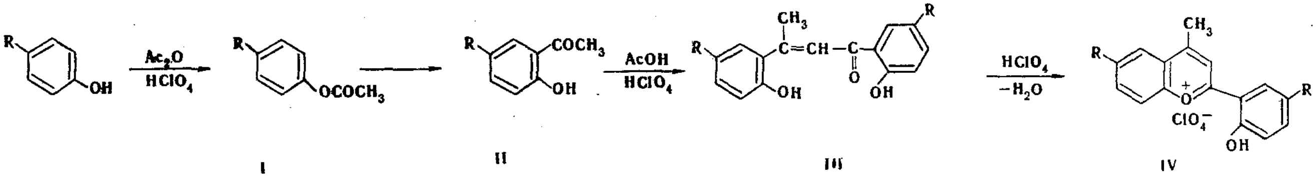
Acylation of phenols with acetic anhydride in the presence of 70% perchloric acid results in the synthesis of hydroxyaryl methyl ketones and substituted benzopyrylium salts.

It is known that acylation of aromatic hydrocarbons and ethers of phenols with acid anhydrides in the presence of 70% perchloric acid leads to 2-alkyl-4,6-diarylpyrylium salts [1,2].

It was not possible to synthesize pyrylium salts from phenols by this method [3], since phenol acetates are obtained by the action of acetic anhydride under mild conditions [4], while reaction with aliphatic acids in the presence of perchloric acid gives o-hydroxyaryl alkyl ketones [5].

In the present research we investigated the acetylation of phenols (phenol, m- and p-cresols, p-thymol, o-xylenol, and resorcinol) with acetic anhydride in the presence of perchloric acid. It was found that the formation of 2-aryl-4-methylbenzopyrylium or 2-methyl-4,6-diarylpyrylium salts was observed along with the formation of o- and p-hydroxyacetophenones when the reaction mixture was heated (100-135°C).

The direction of this reaction depends substantially on the structure of the phenol and the phenol-acetic anhydride-perchloric acid ratio. In the presence of equimolecular amounts of perchloric acid (reagent ratio 1 : 3 : 1), 4-methylflavylium salts (IVa-e, Table 2) are isolated in good yields, and o-hydroxyacetophenones are formed (30-80% yields):



I II III IV

The phenol acetates (I) formed in the first step undergo Fries rearrangement to give o-hydroxyacetophenones (II, Table 1), which, under the reaction conditions, are condensed to chalcones (III), which are further cyclized to 4-methylflavylium salts (IV).

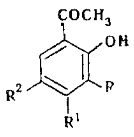
Salts IV are formed readily in the acylation of p-substituted phenols (p-cresol and p-thymol) and are also obtained from those phenolic compounds (m-cresol and o-xylenol) which are converted primarily to o-hydroxyacetophenones during the Fries rearrangement.

Under similar conditions, phenol also gives a low yield (4%) of 4-methyl-2-(2-hydroxyphenyl)benzopyrylium salt (IVe). When 70% $HClO_4$ is introduced into the reaction of o-hydroxyacetophenone with acetic anhydride, the yield of IVe, as expected, increases and reaches 41.6%.

In the case of resorcinol, one observes the formation (in high yield) of resacetophenone or resodiacetophenone, depending on the reagent ratio. 4-Methyl-7-acetoxy-2-(2,4-diacetoxyphenyl)benzopyrylium perchlorate (IVf) is formed from resorcinol in 12.4% yield only when the reagent ratio is 1 : 6 : 0.5.

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 176-180, February, 1974. Original article submitted January 2, 1973.

TABLE 1. o-Hydroxy Ketones



II a-f

Compound	R	R^1	R^2	Phenol-acetic anhydride-perchloric acid molecular ratio	Reaction mixture temp., °C	Reaction time, min	mp, °C bp (mm) *	Yield, %
IIa	H	CH$_3$	H	1 : 3 : 1	125—135	20—30	21	30
IIb	H	H	CH$_3$	1 : 3 : 1	125—135	20—30	50	30
IIc	H	CH$_3$	*i*-(CH$_3$)$_2$-CH	1 : 3 : 1	125—135	30—40	110—115 (7) †	32
IId	CH$_3$	CH$_3$	H	1 : 3 : 1	125—135	40—50	105—110 (7) ‡	35
IIe	H	OH	H	1 : 3 : 1	90—95	40—50	146	70
IIf	H	OH	COCH$_3$	1 : 3 : 0,5	125—135	15—20	182	42

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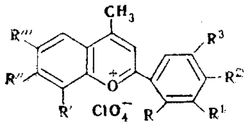
* The melting points and boiling points were in agreement with the data in [10].

† Found,%: C 79.8; H 6.9. $C_{12}H_{15}O_2$. Calculated,%: C 79.6; H 6.7.

‡ Found,%: C 73.3; H 7.4. $C_{10}H_{12}O_2$. Calculated,%: C 73.2; H 7.3.

TABLE 2. 2-Aryl-4-methylbenzopyrylium Perchlorates (IVa-f)



Compound	R	R^1	R^2	R^3	R′	R″	R‴	mp,* °C	Empirical formula	Found, %			Calc., %			IR spectrum, cm^{-1}	Yield, %
										C	H	Cl	C	H	Cl		
IVa	OH	H	CH$_3$	H	H	CH$_3$	H	245—247	$C_{18}H_{17}ClO_6$ †	59,0	4,7	9,4	59,4	4,7	9,7	3250—3200, 1620, 1590, 1520, 1110	55
IVb	OH	H	H	CH$_3$	H	H	CH$_3$	256—258	$C_{18}H_{17}ClO_6$	59,3	4,8	9,4	59,4	4,7	9,7	3300—3220, 1620, 1595, 1540, 1110	44
IVc	OH	H	CH$_3$	*i*-(CH$_3$)$_2$CH	H	CH$_3$	*i*-(CH$_3$)$_2$CH	273—274	$C_{24}H_{29}ClO_6$	64,6	6,3	7,6	64,2	6,5	7,9	1620, 1590, 1540, 1370, 1120	26
IVd	OH	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	H	260—262	$C_{20}H_{21}ClO_6$	60,8	5,5	8,4	61,2	5,3	9,0	3360, 3300, 1620, 1600, 1535, 1105	24
IVe	OH	H	H	H	H	H	H	230—231	$C_{16}H_{13}ClO_6$	57,1	3,9	10,0	57,1	3,9	10,5	3220, 3240, 1620, 1605, 1530, 1120	4
IVf	OCOCH$_3$	H	OCOCH$_3$	H	H	OCOCH$_3$	H	181—182	$C_{22}H_{19}ClO_{11}$ †	53,7	4,0	6,7	53,4	3,8	7,16	1755, 1625, 1545, 1090	12,4

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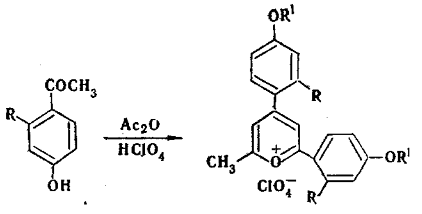
* All of the perchlorates were purified by recrystallization from nitromethane or glacial acetic acid in the presence of a few drops of perchloric acid and melted with decomposition.

† The perchlorates were obtained by alternative synthesis from the corresponding o-hydroxyaryl alkyl ketones.

A confirmation of the proposed scheme for the production of salts IV is the fact that o-hydroxyacetophenones, as a result of self-condensation in acidic media, form the same salts as the corresponding phenols.

The proposed method for the production of 4-methylbenzopyrylium salts differs favorably from the recently developed method for the synthesis of these compounds by condensation of o-hydroxyacetophenones with aliphatic-aromatic ketones [6] with respect to the convenience in the method and the accessibility of the starting phenols.

When p-hydroxyacetophenones are formed in the Fries rearrangement and when there is a free acylium cation in the reaction mixture (1 : 3 : 0.5), the reaction can proceed via a different route to form 2-methyl-4,6-diarylpyrylium salts (V), which are obtained in low yield (5-8%) via the previously studied mechanism of acylation of aromatic compounds and methyl ketones [2].



V a-c

V a R=CH$_3$, R^1=H; b R=H, R^1=COCH$_3$; c R=R^1=H

A confirmation of the indicated scheme is the preparation of Vb from p-hydroxyacetophenone. When the reaction is carried out in the case of phenol, o-acylation of the hydroxyl group of the phenolic residue is observed (by the presence in the IR spectra of an absorption band at 1760 cm^{-1}). Crystallization of Vb from acetic acid (boiling for 2-3 min) leads to hydrolytic splitting out of the acetoxy group to give the perchlorate (Vc). The indicated transformation is accompanied by a change in the color of the salt undergoing crystallization, by the disappearance in the IR spectrum of the band at 1760 cm^{-1}, and by the appearance of an absorption band of an OH group (3320-3330 cm^{-1}) [7].

2-Methyl-4,6-di(4-hydroxyphenyl)pyridine is obtained in 90% yield by treatment of perchlorates Vb,c in excess dilute ammonia solution.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The individuality of the compounds obtained was verified by chromatography in a thin layer of gypsum in benzene–chloroform (7 : 8) [8]. The IR spectra of all of the pyrylium salts obtained contain the absorption bands characteristic for the pyrylium cation and the ClO_4^- anion [9].

4,7-Dimethyl-2-(2-hydroxy-4-methylphenyl)benzopyrylium Perchlorate (IVa) and 2-Hydroxy-4-methylacetophenone. A solution of 10.8 g (0.1 mole) of m-cresol in 30.6 g (0.3 mole) of acetic anhydride was cooled, and 10 ml (0.1 mole) of 70% perchloric acid was added dropwise. The reaction mixture was refluxed carefully at 120-130° for 30-40 min, after which it was diluted with a tenfold excess of ether and allowed to stand in a refrigerator for 2-3 h. The precipitated crystals were removed by filtration to give 10 g (55%) of IVa with mp 245-247° (dec.).

The ether solution was washed with ice water and dried over sodium sulfate. The solvent was removed by distillation, and the residue was steam distilled. The usual treatment of the distillate gave 4 g (27%) of 2-hydroxy-4-methylacetophenone (IIa) with bp 107° (7 mm). The o-hydroxy ketones (IIb-d, Table 1) and perchlorates (IVb-e, Table 2) were similarly obtained.

4-Methyl-2-(2-hydroxyphenyl)benzopyrylium Salts (IVe). A. A 0.68 g (0.005 mole) sample of o-hydroxyacetophenone was refluxed carefully at 120-135° for 20 min in a mixture of 1.5 ml (0.015 mole) of acetic anhydride and 0.5 ml (0.005 mole) of 70% perchloric acid. The mixture was cooled, diluted with ether, and filtered to give 0.35 g (41.6%) of IVe with mp 230-231° (glacial acetic acid).

B. A 0.68 g sample of o-hydroxyacetophenone was refluxed at 120-135° for 30 min in a mixture with 2 ml of acetic acid and 0.5 ml of 70% perchloric acid. The mixture was cooled and diluted with ether to give 0.084 g (10%) of a product; no melting-point depression was observed for a mixture of this product with perchlorate IVe, and their IR spectra were identical.

4-Methyl-7-acetoxy-2-(2,4-diacetoxyphenyl)benzopyrylium Perchlorate (IVf). A 0.5 ml (0.05 mole) sample of 70% $HClO_4$ was added dropwise carefully with cooling to 1.1 g (0.01 mole) of resorcinol dissolved in 6 ml (0.06 mole) of acetic anhydride, and the mixture was heated at 90-95° for 15-20 min. An excess of ether was added, and the mixture was allowed to stand in a refrigerator for 3-4 h. The precipitated oil was reprecipitated two to three times from acetone solution by the addition of ether, after which the addition of a small amount of acetone (1.5-2 ml) gave 0.31 g (12.4%) of colorless crystals of IVf with mp 181-182°.

Resacetophenone. A 1.1 g (0.01 mole) sample of resorcinol was dissolved in 3.1 ml (0.03 mole) of acetic anhydride, after which the solution was cooled and 1 ml (0.01 mole) of 70% perchloric acid was added dropwise. The mixture was heated at 90-95° for 40-50 min, after which it was diluted with water to give 1.06 g (70%) of resacetophenone with mp 146° (mp 146° [10]).

2-Methyl-4,6-di(2-methyl-4-hydroxyphenyl)pyrylium Perchlorate (Va) and 2-Methyl-4-hydroxyacetophenone. A 10.8 g (0.1 mole) sample of m-cresol was dissolved in 30.6 ml (0.3 mole) of acetic anhydride, after which the mixture was cooled, and 5 ml (0.05 mole) of 70% perchloric acid was added. The mixture was then heated at 90-95° for 30-40 min. The resulting pyrylium salt was precipitated with a tenfold excess of ether as a partially crystallized oil. Reprecipitation of the oil from nitromethane or acetic acid gave 1.55 g (7.6%) of perchlorate Va with mp 250-252° (glacial acetic acid). Found,%: C 59.0; H 4.8; Cl 8.5. $C_{20}H_{19}ClO_7$. Calculated, %: C 59.1; H 4.7; Cl 8.7. IR spectrum: 1120, 1534, 1590, 1620, 3250-3270 cm^{-1}. The ether extract was washed with water, and the ether was removed by distillation. The residue was steam distilled, and the new residue was allowed to stand to give 3 g (20%) of 2-methyl-4-hydroxyacetophenone with mp 127° (mp 128° [10]).

2-Methyl-4,6-di(4-acetoxyphenyl)pyrylium Perchlorate (Vb). A. As in the preparation ov Va, Vb was obtained from 0.94 g (0.01 mole) of phenol, 3.06 ml of acetic anhydride, and 0.5 ml (0.005 mole) of perchloric acid by heating the mixture at 95-100° for 10-15 min. The product [0.18 g (8%)] was yellow and had mp 223° (glacial acetic acid). Found, %: C 57.0; H 4.3; Cl 7.6. $C_{22}H_{19}ClO_9$. Calculated, %: C 57.1; H 4.2; Cl 7.7. IR spectrum: 1090, 1540, 1595, 1630, 1760 cm^{-1}.

B. A 3.1 ml (0.03 mole) sample of acetic anhydride and 0.3 ml (0.003 mole) of 70% perchloric acid were added to 1.36 g (0.01 mole) of p-hydroxyacetophenone, and the mixture was heated on a water bath for 1-2 min, after which it was allowed to stand at room temperature for 10-15 min. Cooling and dilution with ether precipitated 0.69 g (30%) of a perchlorate with mp 223° (glacial acetic acid). No melting-point depression was observed for a mixture of this product with perchlorate Vb, and their IR spectra were identical.

2-Methyl-4,6-di(4-hydroxyphenyl)pyrylium Perchlorate (Vc). A 0.4 g sample of perchlorate Vb was refluxed for 2-3 min in glacial acetic acid in the presence of a drop of 70% perchloric acid. The mixture was cooled, diluted with ether, and filtered to give 0.30 g of the perchlorate (Vc) with mp 264-265° (glacial acetic acid). Found: C 57.2; H 4.2; Cl 9.2. $C_{18}H_{15}ClO_7$. Calculated, %: C 57.1; H 4.0; Cl 9.4. IR spectrum: 1120, 1600, 1630, 3320-3330 cm^{-1}.

2-Methyl-4,6-di(4-hydroxyphenyl)pyridine. An excess (4-5 ml) of a 22% ammonium hydroxide solution was added to 0.46 g (0.001 mole) of 2-methyl-4,6-di(4-acetoxyphenyl)pyrylium salt Vb, and the mixture was allowed to stand for several hours. The reaction product was removed by filtration and dried to give 0.25 g (90%) of colorless crystals with mp 276° (from nitromethane). Found, %: C 78.2; H 5.8; N 4.9. $C_{18}H_{15}NO_2$. Calculated, %: C 78.0; H 5.4; N 5.1. IR spectrum: 1520, 1590, 1605, 3380, 3420 cm^{-1}.

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