PHENOLIC DERIVATIVES OF 2-PYRONE. I.

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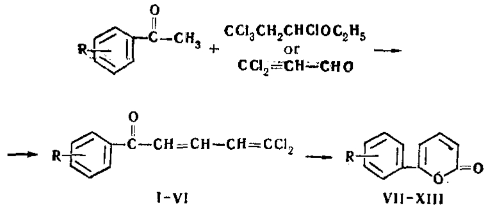
The condensation of hydroxy- and methoxyacetophenones with 1,1,1,3-tetrachloro-3-ethoxypropane or β,β-dichloroacrolein in an acid medium has yielded a number of dichlorodienyl hydroxyphenyl ketones which are converted into the corresponding 2-pyrones in acetic or propionic acids in the presence of phosphoric acid.

The α-pyrone nucleus is a component of a number of natural and synthetic compounds possessing various physiological effects [1, 2, 3]. It appeared of interest to to obtain phenolic derivatives of 2-pyrone and to study the influence of the position of the hydroxy group in the phenolic radical on their physicochemical properties and biological activities.

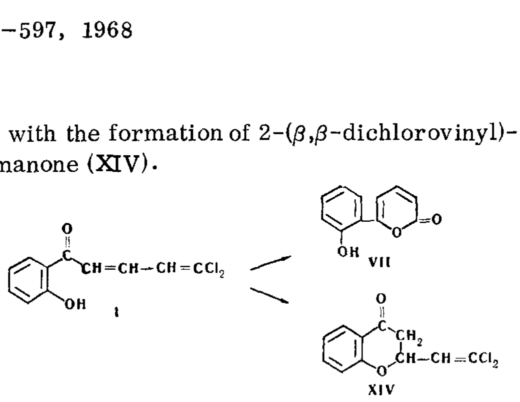
We synthesized 6-(hydroxyphenyl)-2-pyrones by cyclizing the dichlorodienyl ketones (I–VI) which were obtained, in their turn, by condensing hydroxy- and methoxyacetophenones with 1,1,1,3-tetrachloro-3-ethoxypropane (TCEP) or with β,β-dichloroacrolein (DCA) by the following scheme:



I, VII R=o-OH; II, VIII R=o-OCH$_3$; III, IX R=m-OH; IV, X R=m-OCH$_3$; V, XI R=p-OCH$_3$; VI, XIII* R=p-CH$_3$; XII R=p-OH

We found that the synthesis can be carried out in a single stage without the isolation of the dichlorodienyl ketone not only when DCA and 1,1,3-trichloro-3-ethoxypropene are used [4] but also in the case of TCEP; under these conditions the yield of pyrone amounts to 80–90% (Table 2). The hydroxy- and methoxyacetophenones react with TCEP readily even in the cold (Table 1). o-Hydroxyacetophenone is an exception, undergoing only 5–10% reaction under these conditions. The condensation of this compound with DCA at 40–50° C increases the yield of 1,1-dichloro-5-(o-hydroxyphenyl)-1,3-pentadien-5-one to 70–80%.

Heating I–VI in acetic or propionic acid in the presence of phosphoric acid led to the 2-pyrone derivatives (Table 2). However, I can also be cyclized with the participation of the o-hydroxy group of the phenyl nucleus with the formation of 2-(β,β-dichlorovinyl)-4-chromanone (XIV).



Increasing the temperature and time of the reaction raised the yield of VII and lowered the yield of XIV. Substance XIV was colorless (no conjugated system of bonds), did not dissolve in alkalis, and did not give a reaction with ferric chloride solution. A comparison of the IR spectra of I, VII, and XIV confirmed the structure of the latter (see the figure). The IR spectrum of XIV exhibited an absorption band in the 1688 cm^{-1} region due to the stretching vibrations of a C=O group and a characteristic band in the 1643 cm^{-1} region due to the stretching vibrations of an isolated C=C bond of a vinyl group. Moreover, there were strong bands in the 1222 and 1070 cm^{-1} regions corresponding to the stretching vibrations of the =C—O—C— grouping. There were no characteristic bands for the absorption of a hydroxy group whatever. The absence of bands corresponding to the vibrations of an OH group and the displacement of the band of the carbonyl absorption in the direction of shorter wavelengths in the IR spectrum of I is explained by the existence of a hydrogen bond between the carbonyl group and the phenolic hydroxyl. The IR spectrum of VII clearly shows a broad band of associated hydroxy groups with maxima in the 3070 and 3150 cm^{-1} region and a strong absorption band (1712, 1690 cm^{-1}) characteristic for an α-pyrone ring [5, 6].

Compounds I, III, VII, and IX smoothly gave acetyl derivatives with acetic anhydride in the presence of pyridine or sodium acetate. Compounds VIII, X, and XI readily underwent demethylation without the cleavage of the pyrone ring to give VII, IX, and XII, respectively, under the action of aluminum chloride in benzene solution. The o- and p-isomers demethylated more easily than the m-isomer. All the dichlorodienyl ketones (apart from II) and α-pyrones obtained consisted of faintly colored crystalline substances difficult to purify. Compounds II and IV were unstable and decomposed on storage with the evolution of hydrogen chloride.

EXPERIMENTAL

1,1-Dichloro-5-(o-hydroxyphenyl)-1,3-pentadien-5-one (I). Dry hydrogen chloride was passed for 30 min into a mixture of 13.6 g

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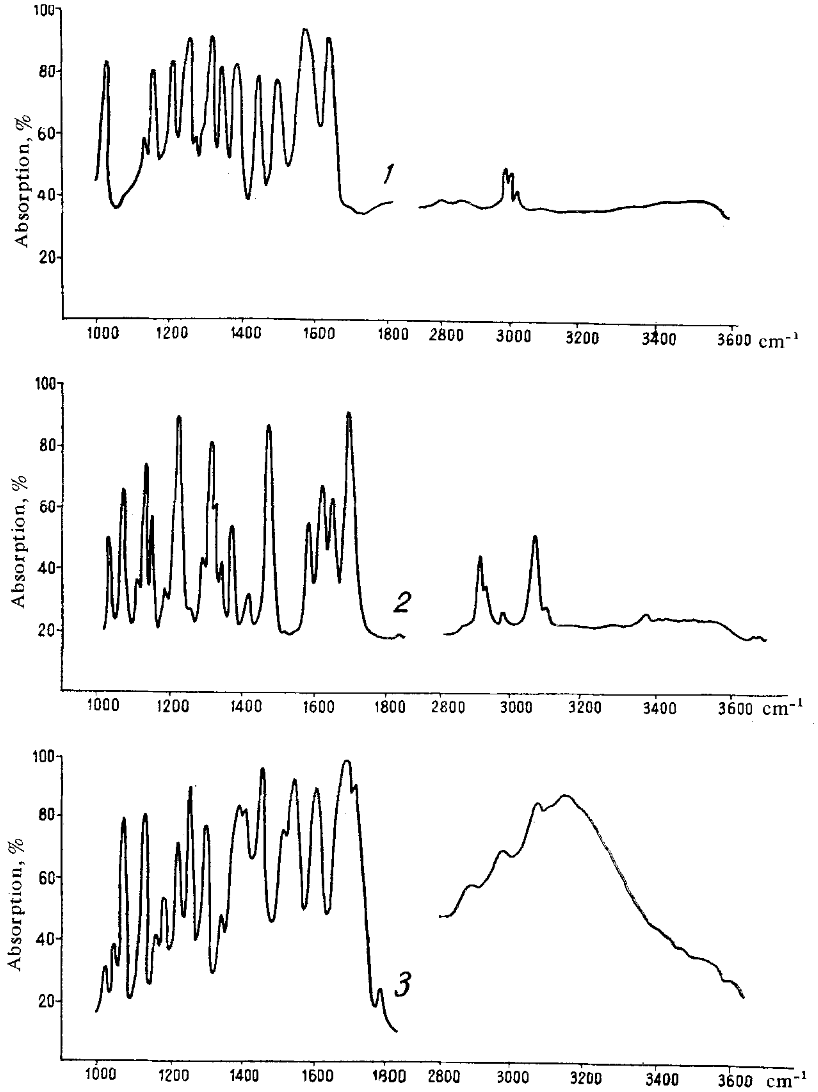
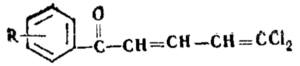
*6-(p-Tolyl)-2-pyrone is synthesized in order to compare its physiological activity with the activities of the hydroxy- and methoxyphenyl-2-pyrones.



IR spectra: 1) 1,1-dichloro-5-(o-hydroxyphenyl)-1,3-pentadien-5-one; 2) 2-(β,β-dichlorovinyl)-4-chromanone; 3) 6-(o-hydroxyphenyl)-2-pyrone.

Table 1



Compound	R	Reaction temperature, ° C	Reaction time, days	Mp, ° C	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
II	*o*-OCH₃	10—15	10	—	$C_{12}H_{10}Cl_2O_2$	—	—	—	—	56.05	3.92	27.58	—	72.7*
	o-OCH₃**	—	—	190—191	$C_{18}H_{14}Cl_2N_4O_5$	—	—	—	12.96	—	—	—	12.81	—
III	*m*-OH	20—25	7	118.5—119.5	$C_{11}H_8Cl_2O_2$	54.47	3.45	29.15	—	54.35	3.32	29.17	—	68.3
	m-OCOCH₃***	—	—	80.5—81.5	$C_{13}H_{10}Cl_2O_3$	54.63	3.39	24.97	—	54.76	3.53	24.87	—	—
IV	*m*-OCH₃	5—10	8	44.5—45.5	$C_{12}H_{10}Cl_2O_2$	55.90	4.01	27.24	—	56.05	3.92	27.58	—	58.5
	m-OCH₃**	—	—	192—192.5	$C_{18}H_{14}Cl_2N_4O_5$	—	—	—	12.88	—	—	—	12.81	—
V	*p*-OCH₃	5—10	15	116.5—117.5[7]	$C_{12}H_{10}Cl_2O_2$	56.21	3.90	28.05	—	56.05	3.92	27.58	—	53.5
VI	*p*-CH₃	5—10	10	98—99[7]	$C_{12}H_{10}Cl_2O$	59.90	4.27	29.54	—	59.77	4.18	29.42	—	48.2

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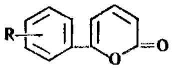
*II could not be purified because of its instability.

**2,4-Dinitrophenylhydrazone.

***Acetate.

Table 2



Compound	R	Method of synthesis	Charged			Time		Mp, °C	Empirical formula	Found, %		Calculated, %		Yield %
			ketone g(mm)	H_3PO_4, ml	CH_3COOH, ml	of standing, days	of boiling, hr			C	H	C	H	
VII	o-OH	A	3 (12.3)	2	45	—	75	196.5—197.5	$C_{11}H_8O_3$	69.84	4.39	70.21	4.28	51.3
VII	o-OH	A	3 (12.3)	1.5	45*	—	26	196.5—197.5	$C_{11}H_8O_3$	70.00	4.14	70.21	4.28	74.0
	o-$OCOCH_3$	—	—	—	—	—	—	74—75	$C_{13}H_{10}O_4$	67.84	4.32	67.82	4.38	—
VIII	o-OCH_3	B	—	2	35	12	16	71.5—72.5	$C_{12}H_{10}O_3$	71.56	5.18	71.28	4.98	91.2
IX	m-OH	A	1 (4.1)	0.5	10	—	20	184—185	$C_{11}H_8O_3$	70.14	4.49	70.21	4.28	81.5
IX	m-OH	B	—	2	35	7	19	184—185	$C_{11}H_8O_3$	70.35	4.61	70.21	4.28	87.7
	m-$OCOCH_3$	—	—	—	—	—	—	118—118.5	$C_{13}H_{10}O_4$	67.82	4.45	67.82	4.38	—
X	m-OCH_3	A	1 (3.9)	0.5	10	—	20	44—45**	$C_{12}H_{10}O_3$	70.84	5.03	71.28	4.98	82.7
X	m-OCH_3	B	—	2	35	7	19	44—45	$C_{12}H_{10}O_3$	70.81	5.01	71.28	4.98	89.2
XI	p-OCH_3	A	8 (31.2)	—	70	—	28	96.5—97.5[7]	$C_{12}H_{10}O_3$	71.52	4.85	71.28	4.98	95.7
XI	p-OCH_3	B	—	2	35	15	25	96.5—97.5	$C_{12}H_{10}O_3$	—	—	71.28	4.98	94.8
XII	p-CH_3	B	—	2	35	10	21	103—103.5[7]	$C_{12}H_{10}O_2$	77.11	5.53	77.40	5.41	82.6

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*Propionic acid.

**Bp 184°-185° C (2 mm).

(0.1 mole) of o-hydroxyacetophenone and 14.5 g (0.116 mole) of DCA at 3°–5° C and then, with the continued passage of hydrogen chloride, the mixture was heated to 40°–45° C for 1 hr 30 min to 2 hr and was kept at this temperature for another 2 hr. Yield 19.3 g (79.4%) (the yields are always given for the unpurified material), mp 143°–143.5° C (ethanol). IR spectrum: 1647, 1579 cm^{-1}. Found, %: C 54.73; H 3.59; Cl 28.82. Calculated for $C_{11}H_8Cl_2O_2$, %: C 54.35; H 3.32; Cl 29.17. Acetate of I, mp 79.5°–80° C (aqueous methanol). Found, %: C 54.35, H 3.77; Cl 24.78. Calculated for $C_{13}H_{10}Cl_2O_3$, %: C 54.76; H 3.54; Cl 24.87.

1, 1-Dichloro-5-(m-methoxyphenyl)-1, 3-pentadien-5-one (IV). A mixture 4 g (0.0266 mole) of m-methoxyacetophenone, 7 g (0.031 mole) of TCEP, and 35 ml of acetic acid was kept at 5°–10° C for 8 days. The brown oil that separated on the addition of water crystallized after some time. Four grams of crystals were separated off and were purified by recrystallization from methanol.

The dinitrophenylhydrazones of II and IV were purified by the chromatography of a solution in carbon tetrachloride on alumina, with subsequent recrystallization from a mixture of benzene and heptane.

Compounds II, III, V, and VI were obtained similarly (Table 1).

6-(o-Hydroxyphenyl)-2-pyrone (VII). A mixture of 3 g (0.0123 ml) of I and 2 ml of 83% phosphoric acid was boiled in 45 ml of glacial acetic acid for 75 hr. The crystals that deposited were separated off and carefully washed with benzene, and the liquid was poured into water. The crystals, consisting of 1.19 g of VII, were recrystallized from water, IR spectrum: 1712, 1690, 3070, 3150 cm^{-1}. The benzene extracts were evaporated in vacuum and diluted with petroleum ether, and, by fractional crystallization and freezing out, white fibrous crystals of the chromanone IV were obtained, with mp 79°–80° C. IR spectrum: 1688, 1222, 1070, 1643 cm^{-1}. Found, %: C 54.34; H 3.32; Cl 28.64. Calculated for $C_{11}H_8Cl_2O_2$, %: C 54.35; H 3.32; Cl 29.17. When the reaction was carried out in propionic acid practically none of the chromanone XIV was formed.

Compounds IV, X, and XI were obtained similarly (Table 2 method A). In the case of X, the reaction mixture was poured into water and extracted with ether and the extract was washed with sodium carbonate solution and with water and was dried with magnesium sulfate. The residue after the elimination of the ether and vacuum distillation crystallized.

6-(m-Hydroxyphenyl)-2-pyrone (IX). A solution of 4 g (0.0294 mole) of m-hydroxyacetophenone and 7.64 g (0.0338 mole) of TCEP in 35 ml of acetic acid was kept at 5°–10° C for 7 days and then 2 ml of 83% phosphoric acid was added and the mixture was boiled for 19 hr and poured into water. This yielded 4.84 g of IX, which was purified by repeated recrystallization from methanol.

Compounds VIII, X, XI, and XIII were also obtained without the isolation of the dichlorodienyl ketone (Table 2, method B).

Demethylation of VIII. With stirring, 0.47 g of aluminum chloride was added to a solution of 0.3 g (0.015 mole) of VIII in 30 ml of benzene. The reaction mixture was heated under reflux for 1 hr and was then decomposed with concentrated HCl. The precipitate was filtered off, washed with benzene, and recrysallized from water or aqueous ethanol. This gave 0.25 g (89.6%), mp 196.5–197.5° C. A mixture with VII exhibited no depression of the melting point

Compounds X and XI were demethylated similarly. The yield of 6-(m-hydroxyphenyl)-2-pyrone was 47.8%, mp 184°–185° C, a mixture with IX giving no depression. The yield of XII was 86.6%. mp 222°–223° C [4].

The IR spectra of I, VII, and XIV were recorded on a UR-10 instrument in the range from 1000 to 1800 cm^{-1} with a sodium chloride prism and in the range from 2800 to 3600 cm^{-1} with a lithium fluoride prism. The substances were compressed into tablets with KBr.

REFERENCES

1. F. Werny and R. Hänsel, Naturwiss., 50, 355, 1963.
2. T. Toda and T. Tokunaga, Chematherapy (Tokyo), 6, 91, 1958; C. A. 52, 20388, 1958.
3. M. J. D. van Dam and F. Kögl, Rec. trav. chim. 83, 39, 1964.
4. L. P. Sorokina and L. I. Zakharkin, Izv. AN SSR, ser. khim., 73, 1964.
5. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL, Moscow, 1963.
6. K. Nakanishi, Absorption Spectroscopy. Practical [Russian translation], Mir, Moscow, 1965.
7. M. Julia and J. Bullot, Bull. soc. chim. France, 28, 1960.

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