SYNTHESIS OF 5,7-DIOXO-6-HALOGENOPHENYL-6,7-DIHYDRO--5*H*-DIBENZO[*a*,*c*]CYCLOHEPTENE DERIVATIVES

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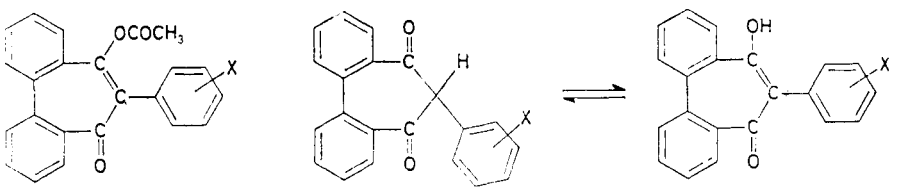
The condensation of diphenic anhydride with *o*-, *m*- and *p*- halogenosubstituted phenylacetic acids gave the respective enolacetates *Ia*—*Ie*. The alkaline hydrolysis of these compounds yields the diketones *IIa*—*IIe*. After testing as blood cloting agents in vivo, the last compounds showed indications of anticoagulants.

It is known that 5,7-dioxo-6-phenyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene *II* (X = H), similar in structure with 2-phenyl-1,3-indandione which is used as anticoagulant in the practice, has a blood cloting activity. The synthesis of different derivatives of the diphenic analogues *II* of 2-phenyl-1,3-indandione is of interest because of the possibility for assessment of the structure–activity relationship of compounds close in structure, but having contrary physiological action.

The aim of the present study was to synthesize some new derivatives of 7-acetoxy--6-halogenophenyl-5-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene (*Ia*—*Ie*) and the respective diketones (*IIa*—*IIe*), as well as to evaluate the physiological activity of some of them.



I *II*

In formulae *I* and *II*: *a*, X = 2-F; *b*, X = 3-F; *c*, X = 4-F; *d*, X = 2-Cl; *e*, X = 3-Cl

The enolacetates *Ia*—*Ie* were synthesized by procedure, similar to that described in ref.[1], via condensation of diphenic anhydride with the respective *o*-, *m*-, or *p*-

-halogensubstituted phenylacetic acid in acetic anhydride, using triethylamine as catalyst. Not so high were the yields of the same compounds isolated by the method described in ref.[2].

The alkaline hydrolysis of enolacetates *Ia–Ie* gave the respective diketones *IIa–IIe* as colourless crystalline substances.

EXPERIMENTAL

The melting points were uncorrected. The IR spectra were taken on a Specord 75 IR spectrophotometer in Nujol oil suspension. All compounds gave satisfactory elemental analyses. The ^{1}H NMR spectra were recorded on Tesla 487 C NMR spectrometer (80 MHz) in deuteriochloroform with tetramethylsilane as an internal standart. The homogeneity of the substances was

TABLE I

Physico-chemical data of compounds *Ia–Ie* and *IIa–IIe*

Compound	X	M.p. °C	Yield %	Formula (M.w.)	Calculated/Found		
					% C	% H	% Cl
Ia	2-F	88–90	17	$C_{23}H_{15}O_3F$ (358·4)	77·08 77·32	4·21 4·47	
Ib	3-F	84–85	42	$C_{23}H_{15}O_3F$ (358·4)	77·08 77·49	4·21 4·09	
Ic	4-F	172–173	25	$C_{23}H_{15}O_3F$ (358·4)	77·08 76·89	4·21 4·15	
Id	2-Cl	92–93	21	$C_{23}H_{15}O_3Cl$ (374·8)	73·70 73·43	4·03 4·09	9·45 9·42
Ie	3-Cl	86–87	24	$C_{23}H_{15}O_3Cl$ (374·8)	73·70 73·45	4·03 4·07	9·45 9·51
IIa	2-F	231–232	84	$C_{21}H_{13}O_2F$ (316·3)	79·73 79·61	4·14 4·19	
IIb	3-F	180–181	87	$C_{21}H_{13}O_2F$ (316·3)	79·73 79·92	4·14 4·15	
IIc	4-F	174–175	82	$C_{21}H_{13}O_2F$ (316·3)	79·73 79·52	4·14 4·18	
IId	2-Cl	227–228	86	$C_{21}H_{13}O_2Cl$ (332·8)	75·79 79·68	3·93 4·07	10·65 10·48
IIe	3-Cl	234–235	88	$C_{21}H_{13}O_2Cl$ (332·8)	75·79 79·71	3·93 3·70	10·65 10·90

checked by TLC on Kieselgel 60 plates, using the following systems: A petroleum ether/ethyl acetate (2 : 1), B chloroform/acetone (9 : 1), C petroleum ether/ethyl acetate (1 : 1), D chloroform/methanol (10 : 1).

7-Acetoxy-6-halogenophenyl-5-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes *Ia*—*Ie*

Diphenic anhydride (1·65 g, 7 mmol), 2 mmol of the respective *o*-, *m*-, or *p*-halogeno substituted phenylacetic acid and 4 ml triethylamine were dissolved in 10 ml acetic anhydride and the mixture was refluxed for 4 h. The dark-brown coloured solution was distilled under reduced pressure and the residue was heated with 200 ml water. After extraction with ethylacetate followed by evaporation, the crude products were recrystallized from ethanol (see Tables I and II).

5,7-Dioxo-6-halogenophenyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes *IIa*—*IIe*

To 1·4 mmol of the respective enolacetate *Ia*—*Ie*, dissolved in 100 ml boiling absolute ethanol, 0·1 g Na in 25 ml ethanol was added. After 90 min stirring at room temperature the solvent was distilled in vacuo. The residue was diluted with 50 ml water, filtered over charcoal and acidified by 6M-HCl. The precipitated crude product was recrystallized from ethanol. The characteristics of the prepared compounds are given in Tables I and II.

TABLE II

R_F values and spectral data of compounds *Ia*—*Ie* and *IIa*—*IIe*

Compound	R_F values[a]		IR, cm^{-1}				Ar-ring *o*-disubst. (4-adjacent Ar-H)
			acetyl CO	CO	C=C	CH_3[b]	
Ia	0·37(A)	0·39(B)	1 732	1 680	1 610	1 370	750, 730
Ib	0·38(A)	0·41(B)	1 746	1 680	1 615	1 372	750, 730
Ic	0·62(A)	0·90(B)	1 770	1 670	1 620	1 370	750, 735
Id	0·31(A)	0·36(B)	1 745	1 680	1 615	1 370	750, 730
Ie	0·33(A)	0·37(B)	1 758	1 680	1 620	1 373	750, 730
IIa	0·15(C)	0·57(D)		1 609			750, 740
IIb	0·23(C)	0·66(D)		1 612			750, 710
IIc	0·32(C)	0·70(D)		1 600			750, 740
IId	0·12(C)	0·70(D)		1 608			750, 740
IIe	0·10(C)	0·55(D)		1 607			750, 740

[a] For the elution systems (in parentheses) see Experimental; [b] in KBr cells.

RESULTS AND DISCUSSION

In the IR spectra of the enolacetates *Ia–Ie* the acetyl C=O stretching bands at 1 776–1 732 cm^{-1} are very intensive. The frequency is increasing because of the vinyl ester structure formation (ref.[3]). There are absorption bands at 1 674 to 1 660 cm^{-1}, due to the keto group in the 7-membered cycle. The absorption of C=C stretching vibrations is observed in the area of 1 613–1 610 cm^{-1}.

In the IR spectra of the compounds *IIa–IIe* the broad absorption bands between 3 400 and 2 300 cm^{-1} correspond to associated hydroxyl groups, appeared as result of the keto–enol tautomerization of *II* (ref.[1]). The lower frequency of the C=O absorption bands at 1 612–1 600 cm^{-1} for *IIa–IIe* indicates tropolone like nature of these compounds (ref.[4]).

For compounds *Ia–Ie* and *IIa–IIe* the frequencies in 750 cm^{-1} region, indicating *o*-disubstituted aromatic ring (4 adjacent Ar-H) are present (ref.[5]).

In the ^1H NMR spectrum of enolacetate *Ib*, a singlet for the methyl protons at δ 2·1 ppm is observed. The multiplet at δ 7·1–7·6 ppm corresponds to the aromatic protons.

The compound *IIc* was tested for coagulant and antitumor activity. It has been established that the substance has comparatively low toxicity (above 400 mg/kg). The coagulant activity was estimated after intraperitoneal administration in mice by the procedure described in ref.[6]. The bleeding time of *IIc* (in dose 300 mg/kg) was 16·8, 7·0 and 5·5 min, respectively, before the administration, 90 and 180 min after the injections.

The antitumor investigations showed that compound *IIc* leads to 27% life prolongation of the mice (type H), contaminated with Leucose L-1210 in comparison with the control group.

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