REACTION OF FLUORINE-CONTAINING β-KETOESTERS WITH BIFUNCTIONAL N-NUCLEOPHILES

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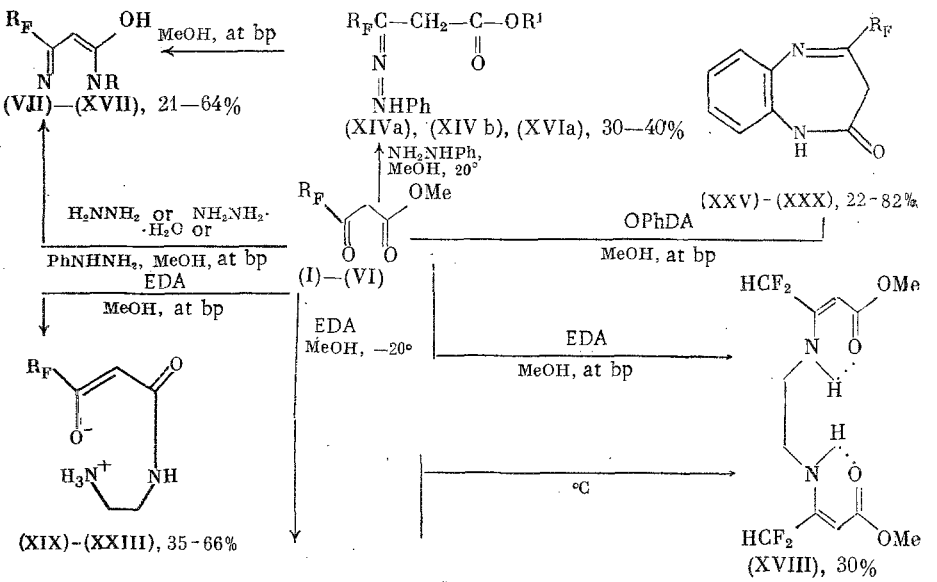
Depending on the type of solvent, with various combinations of temperatures and reagents, fluoroalkyl β-ketoesters (β-FKE) react with nitrogen-containing bifunctional nucleophiles (NBN) at the carbonyl or ester group and also at both these centers, forming heterocycles in the latter instance [1-6]. These reactions were studied in the greatest detail in aprotic solvents [4-6]. However on the basis of the data obtained it is not possible to draw conclusions as the concurrent reactivities of the two nonequivalent electrophilic reaction centers of the β-FKE in proton-donor solvents with respect to the NBN.

Scheme 1



R_F = HCF_2 (I), (VII), (XVIII), (XXIV), (XXV); CF_3 (II), (VIII), (XIII), (XIX), (XXVI); $H(CF_2)_2$ (III), (IX), (XIVa, b), (XX), (XXII); C_3F_7 (IV), (X), (XV), (XXI), (XXVIII); $H(CF_2)_4$ (V), (XI), (XVI), (XVIa), (XXII), (XXIX); C_4F_9 (VI), (XII), (XVII), (XXIII), (XXX); R = H (VII)—(XII); R^1 = Me (XIVa); Et (XIVb), (XVIa),

We have studied the reactions of β-FKE's (I)-(VI) (Scheme 1) with hydrazine, hydrazine hydrate, phenylhydrazine, ethylenediamine (EDA) and o-phenylenediamine (OPhDA) in methanol.

Boiling β-FKE's (I)-(VI) with hydrazine hydrate or phenylhydrazine in methanol yields pyrazolones (VII)-(XVII) (see Scheme 1, Table 1). Only in the case of phenylhydrazine at ∿20°C phenylhydrazones (XIVa, b), (XVIa) are formed (see Table 1) which cyclize to pyrazolones on boiling the reaction mixture. In the IR spectra of (VII)-(XII) obtained from β-FKE's (I)-(VI) and hydrazine or hydrazine hydrate were the bands $\nu_{C=C}$ 1600-1605, ν_{CN} 1570, and ν_{OH} 2200-2700 cm^{-1} and the amide band as absent (see Table 1). In the PMR spectra of the compounds resonance signals of the methine protons are present, δ_{CH} = 5.9-6.1 ppm and the NH and OH signals δ = 7.03-11.4 ppm integrated for two protons which is evidence for the existence of compounds (VIII)-(XII) in the hydroxy form. This substantiates the results of reference [2] but not those of [1] in which the structure of 5-trifluoromethylpyrazolin-3-one has been studied. N-Phenyl substituted pyrazolones (XIII-XVII) also exist in the hydroxy form according to the IR and PMR spectra (see Table 1).

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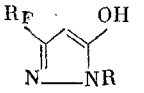
TABLE 1. Fluoroalkyl-Containing Pyrazolones



Compound	R_F	R	Mp, °C (solvent)	Yield, %	Found / Calculated, % C	H	N	F	Molecular formula	IR spectrum, ν, cm⁻¹ C=C	NH	OH	PMR spectrum (δ, ppm from TMS, solvent acetone-d_6) CH	NH OH	H $(CF_2)_n$, J_{HCF_2}, $J_{H(CF_2)_2}$ Hz
(VII)	HCF_2	H	150–151 (benzene)	43	35,93 / 35,85	2,81 / 3,01	20,59 / 20,89	27,63 / 28,43	$C_4H_4F_2N_2O$	1605	1530 3290	2200 2700	5,72	8,9	6,64 t; J=55,0
(VIII)	CF_3	H	135–137 (xylene)	64	31,52 / 31,59	1,82 / 1,99	18,70 / 18,42	36,67 / 37,48	$C_4H_3F_3N_2O$	1605	1540 3220	2200 2700	5,77	11,00	–
(IX)	$H(CF_2)_2$	H	140–141 (xylene)	30	32,87 / 32,62	2,85 / 2,20	15,30 / 15,22	41,22 / 41,28	$C_5H_4F_4N_2O$	1600	1550 3200	2100 2700	5,93	11,0	6,62 t, t; J=55,9, 5,1
(X)	C_3F_7	H	138–140 (xylene)	63	28,04 / 28,59	1,70 / 1,20	10,50 / 11,11	52,67 / 52,75	$C_6H_3F_7N_2O$	1600	1520 3285	2200 2700	5,83	7,03	
(XI)	$H(CF_2)_4$	H	166–168 (xylene)	21	29,04 / 29,50	1,22 / 1,42	10,30 / 9,96	53,27 / 53,49	$C_8H_4F_8N_2O$	1595	1540 3240	2200 2700	5,86	11,4	6,71 t, t; J=51,4, 5,7
(XII)	C_4F_9	H	141–143 (benzene)	31	27,45 / 27,83	1,12 / 1,00	9,02 / 9,27	56,45 / 56,00	$C_8H_3F_9N_2O$	1595	1540 3240	2200 2700	5,8	11,10	–
(XIII)	CF_3	Ph	166–168 (heptane)	21	52,67 / 52,64	2,87 / 3,09	12,22 / 12,28	33,92 / 24,98	$C_{10}H_7F_3N_2O$	1600	–	2200 2800	5,83	7,80	–
(XIV) *	$H(CF_2)_2$	Ph	157–159 (heptane)	53	50,94 / 50,78	3,04 / 3,10	10,68 / 10,77	28,77 / 29,21	$C_{11}H_8F_4N_2O$	1600	–	2200 2700	5,91	7,50	6,44 t, t; J=56,6, 5,2
(XIVa) †	$H(CF_2)_2$	Ph	65–66 (hexane)	44	49,17 / 49,32	4,02 / 4,14	9,64 / 9,59	26,03 / 26,00	$C_{12}H_{12}F_4N_2O_2$	C=N 1600	1520 3330	C=O 1750	3,72 ‡	9,6	6,8 t, t; J=52,7, 6,0
(XIVб) †	$H(CF_2)_2$	Ph	58–59 (hexane)	30	50,87 / 50,98	4,34 / 4,60	9,30 / 9,14		$C_{13}H_{14}F_4N_2O_2$	C=N 1600	1510 3220	C=O 1700	3,73 ‡ 3,15 (OEt)	9,7	6,70 t, t; J=53; 6,7
(XV)	C_3F_7	Ph	150–152 (heptane)	52	43,68 / 43,92	2,51 / 2,15	8,51 / 8,54	40,13 / 40,52	$C_{12}H_7F_7N_2O$	1600	–	2200 2800	5,94	7,5	–
(XVI)	$H(CF_2)_4$	Ph	151–153 (benzene)	61	42,84 / 43,35	2,61 / 2,24	7,38 / 7,78	41,70 / 42,19	$C_{13}H_8F_8N_2O$	1600	–	2200 2700	6,03	7,60	6,75 t, t; J=55,4; 4,57
(XVIa) †	$H(CF_2)_4$	Ph	112–114 (hexane)	31	44,40 / 44,46	2,7 / 3,23	7,0 / 6,91		$C_{15}H_{14}F_8N_2O_2$	C=N 1600	1510 3330	C=O 1720	3,75 ‡ 3,15 (OEt)	10,1	6,8 t, t; J=55,4; 4,57
(XVII)	C_4F_9	Ph	157–159 (benzene)	52	41,07 / 41,29	2,16 / 1,87	7,18 / 7,41	45,72 / 45,21	$C_{13}H_7F_9N_2O$	1600	–	2150 2800	6,18	7,50	–

*Spectrum taken in $CDCl_3$.

† $H(CF_2)_4C(=NNHPh)CH_2CO_2Me$ (XVIa), $H(CF_2)_4C(=NNRPh)CH_2CO_2Et$ (XIVb), $H(CF_2)_4CH_2C(=NNHPh)CO_2Et$ (XVI a)

‡ The signals of the CH_2 group are shown.

TABLE 2. Products of Reaction of β-FKE's with EDA

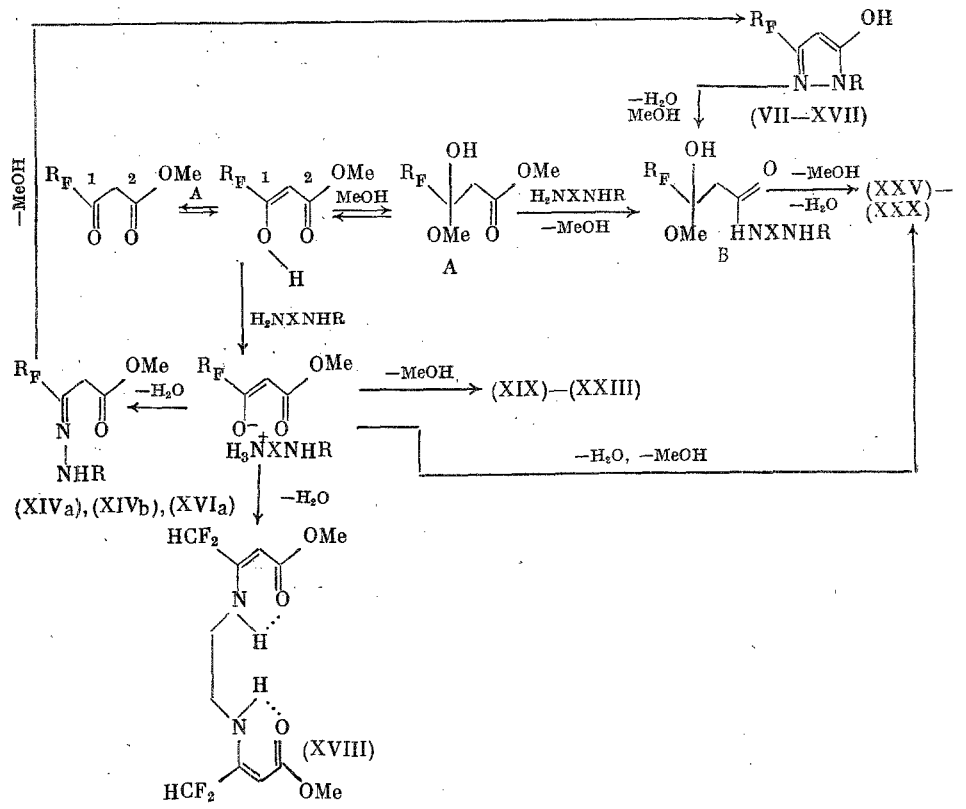
Compound	Yield, %	Mp, °C (solvent)	Found/Calculated, %				Molecular formula	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm from HMDS, solvent, DMSO-d_6			
			C	H	N	F		C=O	NH	N^+H_3	CH_2	CH	NH	$H(CF_2)_n$, J_{HCF_2}, $J_{H(CF_2)_2}$, Hz
(XVIII)	30	108–109 CCl_4	44,11 43,91	4,89 4,91	8,14 8,53	23,00 23,15	$C_{12}H_{16}F_4N_2O_4$	1680	1620 3330		2,92 3,53	4,97	8,5	6,17 t J=55,9
(XIX) *	35	170–172 methanol	35,72 36,37	4,14 4,68	14,20 14,14	28,50 28,76	$C_6H_6F_3N_2O_2$	1650	1615	1465 1590 2300 2800	2,9 3,42	4,8	–	
(XX)	37	189–191 methanol, ether	36,57 36,53	5,18 4,38	12,50 12,17	32,58 33,02	$C_7H_{10}F_4N_2O_2$	1640	1620 3280	1420 1575 2300 2700	2,91 3,4	4,7	4,3	6,68 t. t J=55,9, 5,52
(XXI)	50	209–211 benzene	32,37 32,23	3,21 3,04	9,50 9,40	43,80 43,60	$C_8H_9F_7N_2O_2$	1640	1620 3260	1420 1570 2300 2800	2,91 3,49	4,7	5,6	–
(XXII)	66	208–210 d. methanol, ether	32,51 32,74	3,54 3,05	8,00 8,49	45,52 46,03	$C_9H_{10}F_8N_2O_2$	1640	1620 3280	1470 1580 2400 2800	2,85 3,5	4,7	4,9	6,60t. t J=56,6, 5,2
(XXIII)	60	209–211 (CCl_4)	31,45 31,05	2,43 2,61	7,94 8,05	49,01 49,11	$C_9H_9F_9N_2O_2$	1640	1620 3270	1470 1570 2200	2,9 3,4	4,68	4,4	–
(XXIV) †	17	–	39,70 39,56	5,75 5,53	7,95 7,69	–	$C_{12}H_{20}F_4N_2O_6$	1680	1620 3320	1475	3,02 3,06 3,8(OMe)	5,05	7,9	6,17t J=55,0

*PMR spectra in D_2O.
†PMR spectrum in acetone-d_6.

TABLE 3. Fluoroalkyl-Containing Benzodiazepinones

Compound	Yield, %	Mp, °C (solvent)	Found/Calculated, %				Molecular formula	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm from HMDS, solvent, DMSO-d_6			
			C	H	N	F		C=O	NH	CH_2	NH	$H(CF_2)_n$, J_{HCF_2}, $J_{H(CF_2)_2}$, Hz	Ph
(XXV)	22	210–212 (hexane)	57,22 / 57,14	3,86 / 3,84	13,86 / 13,33	17,73 / 18,08	$C_{10}H_8F_2N_2O$	1680	1485 3130 3215	3,47	9,50	6,41 t J=53,4	7,62
(XXVI)	82	183–184 (benzene)	53,30 / 52,64	3,19 / 3,09	12,61 / 12,28	24,85 / 24,98	$C_{10}H_7F_3N_2O$	1690	1480 3140 3220	3,38	9,50	–	7,4
(XXVII)	38,5	168–170 (pentane)	50,53 / 50,78	2,96 / 3,09	10,67 / 10,77	29,27 / 29,21	$C_{11}H_8F_4N_2O$	1695	1485 3150 3240	3,40	9,40	6,56 t.t J=52,4 4,8	7,5
(XXVIII)	37	142–144 (hexane)	43,91 / 43,92	2,35 / 2,15	8,62 / 8,54	40,57 / 40,52	$C_{12}H_7F_7N_2O$	1690	1490 3145 3235	3,45	9,65	–	7,65
(XXIX)	52	145–147 (hexane)	43,39 / 43,35	2,05 / 2,24	7,72 / 7,78	42,8 / 42,22	$C_{13}H_8F_8N_2O$	1690	1485 3100 3200	3,43	9,80	6,32 t.t J=54,6, 5,4	7,61
(XXX)	22	146–148 (hexane)	40,83 / 41,29	1,70 / 1,87	7,32 / 7,41	46,12 / 46,24	$C_{13}H_7F_9N_2O$	1680	1400 3214 3220	3,46	9,40	–	7,55

Scheme 2



In the PMR spectra of compounds (XIVa), (XVIb), (XVIa) (see Table 1) are found signals at 3.86 (MeO), 3.72-3.75 (CH_2), and 9.6-10.1 ppm (NH) verifying their hydrazone structure.

The reaction of β-FKE's (I)-(VI) with EDA in methanol proceeds ambiguously and depends on the type of fluoroalkyl radical (R_F). Thus β-FKE (I) (R_F = CHF_2) with a (1:1) ratio of (I):EDA yields the 3,3'(N,N'ethylenediamine)-bis-4-difluoro-2-buteonate ester (XVIII) (see Scheme 1, Table 2). An analogous reaction is characteristic of acetoacetic ester [3]. In the IR spectrum of (XVIII) are bands 1680 (CO) and 1620-3330 (NH) cm^{-1}, and in the PMR spectrum signals 2.92 (CH_2), 4.97 (CH), 3.76 (MeO), and 8.5 (NH) ppm.

In contrast to the above, β-FKE's (II)-(VI) with EDA form internal amine salts of the aminoethylamide with the enol group (XIX-XXIII) as the only products (see Scheme 1, Table 2). According to the data of [4] trifluoroacetoacetic ester with EDA in xylene yields a mixture of 1,2,3,4-tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one and 2-trifluoromethyl-2-imidazolidine acetate. On reaction of β-FKE (R_F = C_2F_5) with EDA in benzene with EDA an analogous inner salt of the amide, N-(2-aminoethyl)-4,4,5,5,5,-pentafluoro-2-pentamide along with 2-(pentafluoroethyl)-2-imidazolidine acetate, and the ethylene diamine salt are formed [5].

In the IR spectra of (XIX)-(XXIII) are found bands characteristic of the groups CONH, NH, and NH_3^+: 1640, 1620, and 3270, 1470-1485, 1570, 2300-2800 cm^{-1} respectively.

In the PMR spectra of these compounds the signals 2.9-3.4 (CH_2), 4.7 (CH), and 4.3-5.6 (NH) ppm are observed.

On carrying out the reaction of β-FKE (I), (R_F = HCF_2) with EDA in a 1:1 ratio at −20°C in methanol the 2:1 salt (XXIV) was isolated (see Scheme 1, Table 2) which on increasing the temperature of the mixture goes over to compound XVIII and is evidently an intermediate product in the reaction of the β-FKE with EDA.

β-KFE's (I)-(VI) with OPhDA in methanol form only 4-(fluoroalkyl)-1H-1,5-benzodiazepin-2-ones (XXV)-(XXX) (see Scheme 1, Table 3), just as it was found for trifluoroacetoacetic ester in reactions in neutral or weakly basic media [6]. In the IR spectra of compounds (XXV)-(XXX) there are bands at 1675-1690 (CO), and 1650-1660, 3100-3240 cm^{-1} (NH). In the PMR spectra of these compounds are signals at 3.38-3.46 (CH_2), and 9.4-9.8 ppm (NH), which is evidence for the amide form of compounds (XXV)-(XXX).

It can be surmised that the reaction of β-FKE with NBN proceeds in at least the two directions presented in Scheme 2. Firstly the explanation of the synthesis of all the types of compounds obtained is included in the initial formation of salts of type (XXIV) by reaction with the enol form of β-FKE and in subsequent processes either replacing the methoxyl group (XIX)-(XXIII), or undergoing both of the indicated processes which lead to heterocyclic compounds (VII)-(XVII) and (XXV)-(XXX). In favor of the suggestion regarding this pathway for the reaction is the formation of the salt (XXIV) from β-FKE (I) (R_F = HCF_2) and EDA, which was successfully isolated on carrying out the reaction at −20°C, and also the formation of hydrazones (XIVa), (XIVb), (XVIa) from β-FKE's and phenylhydrazine. However we can not completely exclude the possibility of a second reaction pathway, inasmuch as we have previously shown that β-FKE's form type A adducts [7] with methanol in deuteroacetone. This route can not lead to compounds of type (XVIII), nevertheless products (VII)-(XVII), (XIX)-(XXIII), and (XXV)-(XXX), can be obtained along with it by means of intermediate compounds of type B. Utilization of these pathways depends on the acidity of the β-FKE, the electrophilicity of the reaction centers 1 and 2 of β-FKE and the basicity of the NBN reacting.

EXPERIMENTAL

The PMR spectra were obtained on a Perkin-Elmer R-12B (60 MHz) apparatus, the IR spectra on a UR-20 spectrophotometer in a mineral oil mull. All β-FKE's were obtained according to the method described in [8].

Fluoroalkyl Pyrazolones (VII)-(XVII). To a boiling solution of 50 mmoles of β-FKE in 150 ml methanol an equivalent amount of the hydrazine (hydrazine hydrate, phenylhydrazine) in 15 ml MeOH was added dropwise in a stream of Ar, the mixture refluxed 6 h in a stream of Ar, then the solvent was removed in a vacuum. The residue was recrystallized, obtaining pure pyrazolones (VII)-(XVII). The yield and the physicochemical constants are shown in Table 1.

3-(N-Phenyl)hydrazones of Fluorocarboxylic Esters (XIVa), (XIVb), (XVIa). To a solution of 60 mmoles of β-FKE in 150 ml CH_3OH was added in a stream of Ar 60 mmoles of phenylhydrazine in 30 ml MeOH, the mixture refluxed 1 h in a stream of Ar, poured into water (250-300 ml) and extracted with two 75 ml portions of ether, the ether was distilled off, the residue recrystallized from hexane. The yield and constants are shown in Table 1.

Reaction of β-FKE with EDA. To a solution of 30 mmoles of β-FKE in 100 ml MeOH was added an equivalent amount of EDA in 30 ml MeOH. The reaction mixture was refluxed 25-30 h in a stream of Ar (in the case of compound (XXIV) the reaction was carried out at −20°C). The solvent was distilled off in a vacuum. To the residue was added 20-50 ml dry ether, the crystals formed were filtered off and washed with ether (2 × 20 ml). The yields and constants are shown in Table 2.

4-Fluoroalkyl-1H-1,5-Benzodiazepin-2-ones (XXV)-(XXX). To a solution of 30 mmoles β-FKE in 100 ml MeOH an equivalent amount of OPhDA in 100 ml MeOH was added dropwise in a stream of Ar. The mixture was refluxed in a stream of Ar for 4-6 h, the solvent distilled off in a vacuum, the residue recrystallized, obtaining the pure benzdiazepinone. The yields and constants are shown in Table 3.

CONCLUSIONS

1. Fluoroalkyl β-ketoesters with phenylhydrazine at 20°C form phenylhydrazones of the β-ketoesters, which form hydroxypyrazoles on heating.

2. 4,4-Difluoroacetoacetic ester with ethylenediamine yields the 3,3'-(N,N'-ethylenediamine)-bis-4,4-difluoro-2-butenoate ester whereas on lengthening the fluoroalkyl substituent internal salts of the aminoethylamides of the β-keto acids are formed from the β-ketoesters.

3. Hydrazine and o-phenylenediamine react with fluorine-containing β-ketoesters with the formation of pyrazoles and benzodiazepinones respectively.

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CHLORINE SUBSTITUTED 2-(4'-DIMETHYLAMINOPHENYL)INDAN-1,3-DIONES AND THEIR DIMERS

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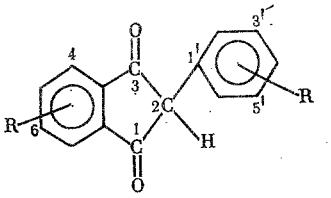
Cyclic β-diketones, the best known representative of which is 2-phenylindan-1,3-dione (Ia) and also its derivatives having substituents on the aromatic rings on the second carbon atom have various biological and chemical activities [1, 2].

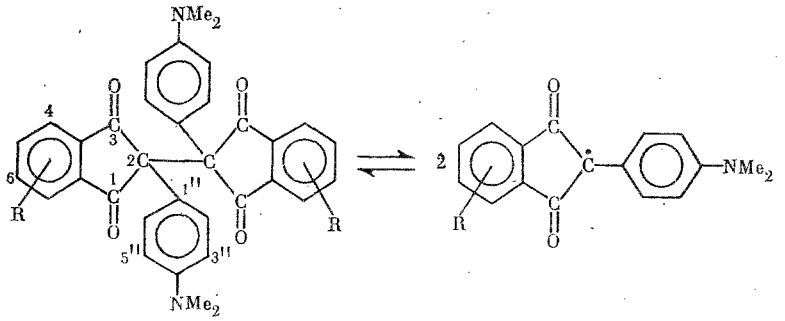
It has been shown that the introduction of a Cl atom into the phenyl or phthaloyl ring appreciably influences the nature of the biological action of the preparation [3].



(Ia-d)

R = R′ = H (a); R = 4-Cl, R′ = 4′-N(Me)$_2$ (b); R = 5-Cl, R′ = 4′-N(Me)$_2$ (c); R = H, R′ = 4′-N(Me)$_2$ (d)

In work [4] was established the strong inhibiting action of 2-(4'-dimethylaminophenyl)-indan-1,3-dionic free radicals generated by the decomposition of the dimer 2,2'(bis(4"-dimethylaminophenyl)indan-1,3-dione (IIa) in the low temperature oxidation reactions of hydrocarbons.



(IIa-c)

R = H (a), 4-Cl (b), 5-Cl (c).

In the work in question new 2-arylindan-1,3-diones (Ib, c) containing chlorine in the phthaloyl ring and the corresponding dimers (IIb, c) were synthesized.

Normally halogen substituted 2-arylindan-1,3-diones are obtained by an anhydride condensation method, i.e., heating the corresponding halophthalic anhydride in an arylacetic

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