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SYNTHESIS AND PROPERTIES OF HALOGENATED DERIVATIVES OF DIBENZO-p-DIOXINE CONTAINING A TRIFLUOROMETHYL GROUP

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Methods of preparation of a series of polyhalogenated dibenzo-p-dioxines containing the trifluoromethyl group in the 2 position are described. The physicochemical properties of these compounds are studied, electron impact mass spectra are discussed, and relative retention times are measured. In their gas-chromatographic and mass-spectral characteristics, some of the synthesized compounds are suited for use as internal standards in the quantitative determination of polychlorinated dibenzo-p-dioxines and dibenzofurans in the environment by means of the chromato-mass-spectrometric method.

It is well known that polyhalogenated dibenzo-p-dioxines are among the most dangerous environmental pollutants [1], having a very broad range of effects on the biota [2, 3], and although polychlorinated dibenzo-p-dioxines are the chief pollutants observed in the environment, there have been reports of the presence of compounds with bromine atoms and nitro groups as substituents [4]. Apparently, other dibenzodioxines containing functional groups can also be observed. Data on the physicochemical properties of such compounds are very limited [5], and therefore, the study of halogenated compounds of this class, containing various functional groups, is of major interest. We have synthesized a series of dibenzodioxines that, in addition to chlorine and bromine atoms, contain the trifluoromethyl group in the 2 position, and studied their physicochemical, gas-chromatographic and mass-spectral properties. It was proposed to use the synthesized compounds VIa-f as internal standards both in sample preparation for chromato-mass-spectrometric (CMS) analysis and for quantitative measurements in the CMS method [6]. Compounds containing a fluoromethyl group do not exist in nature as xenobiotics and cannot produce background noise in analytical measurements.

The synthesis of trifluoromethyl derivatives of dibenzo-p-dioxine is based on the condensation reaction of dipotassium salt of pyrocatechol Ia or its dichloro(dibromo) derivative Ib, with the corresponding o-nitrohalosubstituted trifluoromethylbenzenes IIa, b in DMFA or absolute acetone. The crown ether 18-crown-6 was used as the catalyst.

The characteristics of the synthesized trifluoromethyl derivatives of dibenzo-p-dioxine are shown in Table 1, and the synthesis condition, in Table 2.

Formation of the tricyclic structure of dibenzo-p-dioxine proceeds via formation of the intermediate diphenyl ether IIIa-f, product of the reaction of the phenoxy anion Ia-c with the o-nitrohalo derivative compound IIa, b [7]. As a result of an intramolecular reaction, the ether formed forms the σ complex IVa-f (Meisenheimer's spiral complex). A subsequent Smiles rearrangement [8] leads to the formation of a second ether, Va-f. The identical nature of R^1 and R^2 and their symmetric arrangement with respect to R^3 and CF_3 preclude the formation of a mixture of halogenated isomers of 2-trifluoromethyldibenzo-p-dioxine VIa-f, as was confirmed by the chromato-mass-spectrometric method.

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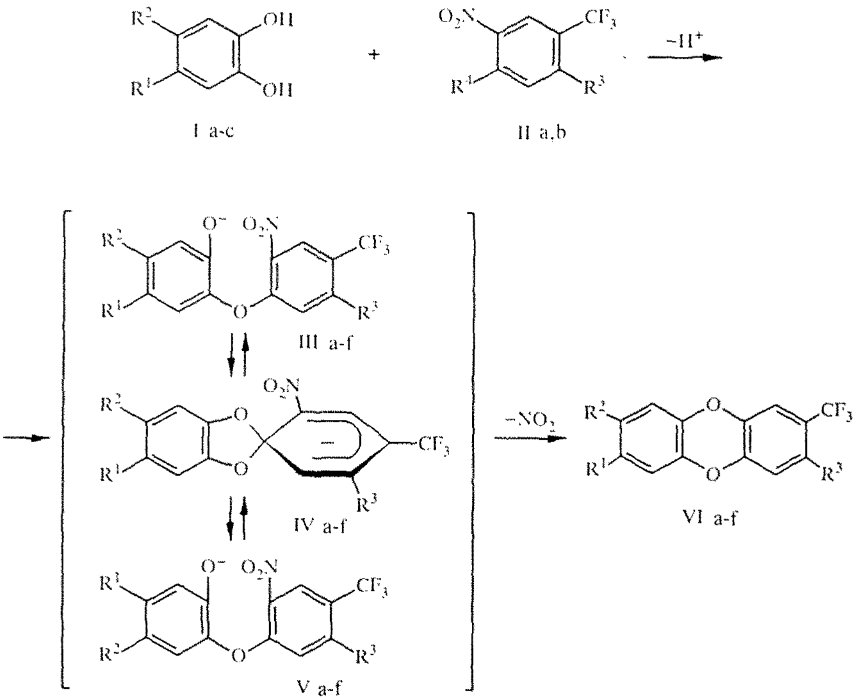
TABLE 1. Physicochemical Properties of Compounds VIa-f

Compound	R^1	R^2	R^3	Empirical formula	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)
VIa	H	H	H	$C_{13}H_7F_3O_2$	107...108	3050 (C—H), 1595, 1500 (C=C), 1330 (C—O—C), 1110 (C—F)	6,99 (4H, m, 6-H, 7-H, 8-H, 9-H); 7,10 (1H, d.q., 4-H, $J_{3,4}$ =8,1); 7,22 (1H, d.q, 1-H, $J_{1.3}$ = 1,9); 7,29 (1H, d.q, 3-H)
VIb	H	H	Cl	$C_{13}H_6ClF_3O_2$	130...132	3030 (C—H), 1585, 1495 (C=C), 1330 (C—O—C), 1105 (C—F), 750 (C—Cl)	7,01 (4H, m, 6-H, 7-H, 8-H, 9-H); 7,21 (1H, dd, 4-H, $J_{1.4}$ = =0,3); 7,32 (1H, q, 1-H)
VIc	Cl	Cl	H	$C_{13}H_5Cl_2F_3O_2$	103...104	3060 (C—H), 1580, 1485 (C=C), 1330 (C—O—C), 1110 (C—F)	7,13 (1H, d.q 4-H, $J_{3,4}$ = 8,4); 7,19, 7,21 (2H, d, 6-H, 9-H, $J_{6,9}$ = 0,3); 7,25 (1H, d.q, 1-H, $J_{1.3}$ = =2,1); 7,38 (1H, d.q 3-H)
VId	Br	Br	H	$C_{13}H_5Br_2F_3O_2$	99...100	3040 (C—H), 1575, 1475 (C=C), 1320 (C—O—C), 1115 (C—F), 725 (C—Br)	7,14 (1H, d.q 4-H, $J_{3,4}$ = 8,4); 7,26 (1H, d.q, 1-H, $J_{1.3}$ = =1,6); 7,32, 7,33 (2H, d, 6-H, 9-H, $J_{6,9}$ = 0,2); 7,39 (1H, d.q 3-H)
VIe	Cl	Cl	Cl	$C_{13}H_4Cl_3F_3O_2$	180...182	3080 (C—H), 1570, 1465 (C=C), 1325 (C—O—C), 1135 (C—F)	7,23, 7,25 (2H, d, 6-H, 9-H, $J_{6,9}$ = 0,3); 7,28 (1H, dd, 4-H, $J_{1,4}$ = 0,6); 7,30 (1H, dd, dd, 1-H)
VIf	Br	Br	Cl	$C_{13}H_4Br_2ClF_3O_2$	204...206	3080 (C—H), 1570, 1470 (C=C), 1310 (C—O—C), 1140 (C—F)	7,27 (1H, dd, 4-H); 7,35 (1H, dd, 1-H); 7,37 (2H, dd, 6-H, 9-H, $J_{6,9}$ = 0,6)



I,a-c a $R^1=R^2=H$, b $R^1=R^2=Cl$, c $R^1=R^2=Br$; IIa,b,a $R^3=H$, $R^4=Br$; b $R^3=R^4=Cl$; III, IV, V, VI a $R^1=R^2=R^3=H$; b $R^1=R^2=H$, $R^3=Cl$; c $R^1=R^2=Cl$, $R^3=H$; d $R^1=R^2=Br$, $R^3=H$; e $R^1=R^2=$ $=R^3=Cl$; f $R^1=R^2=Br$, $R^3=Cl$

TABLE 2. Conditions of Preparation of Compounds VIa-f

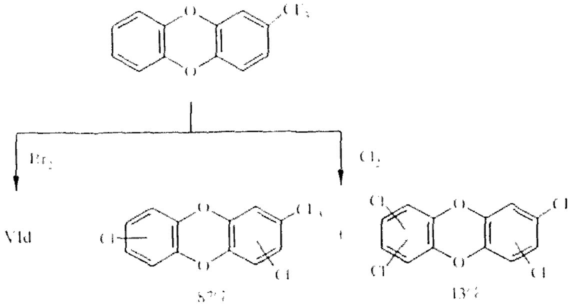
Compound	Solvent, ml	Molar ratio of starting components				Solvent for recrystallization	Yield, %
		Ia-c	IIa, b	potassium carbonate	18-crown-6		
VIa	DMFA 50	0,02	0,02	0,1	0,002	Methanol – water (85:15)	92
VIb	Acetone, 100	0,027	0,027	0,134	0,0024	Heptane, twice	26
VIc	DMFA, 55	0,016	0,016	0,08	0,0015	Heptane, acetic acid – water (1:1) with activated carbon	86
VId	DMFA, 55	0,012	0,012	0,061	0,0012	Hexane, acetic acid – water (1:1) with activated carbon	30
VIe	Acetone, 70	0,016	0,016	0,08	0,0015	Decane	41
VIf	Acetone, 70	0,012	0,012	0,057	0,0011	Decane	60

TABLE 3. Solubility of Compounds VIe Compared with 2,3,7,8-Tetrachlorodibenzo-p-dioxine (TCDD)

Compound	Solubility (g/liter) at 205°C in the solvents				
	DMSO	o-xylene	chloroform	1,4-dioxane	benzene
VIe	1,2	28,4	32,1	14,2	28,2
VIf	1,1	29,1	23,0	13,2	30,9
2,3,7,8-TCDD	0,2	—	0,6	1,5	0,5

By reacting pyrocatechol with 4-bromo-3-nitro-1-trifluoromethylbenzene, we obtained 2-trifluoromethyldibenzo-p-dioxine VIa. Addition of 4,5-dichloro- or 4,5-dibromopyrocatechol to the reaction led to the formation of 7,8-dichloro-2-trifluoromethyl- VIc and 7,8-dibromo-2-trifluoromethyldibenzo-p-dioxine VIc and 7,8-dibromo-2-trifluoromethyldibenzo-p-dioxine VId, respectively. Laterally substituted 2-trifluoromethyl-3,7,8-trichloro VIe and 7,8-dibromo-2-trifluoromethyl-3-chlorodibenzo-p-dioxines VIf were obtained by reacting 2,3-dichloro-5-nitro-1-trifluoromethylbenzene with 4,5-dichloro- and 4,5-dibromopyrocatechol. Addition of unsubstituted pyrocatechol to the reaction formed a monochlorinated derivative of dibenzo-p-dioxine VIb, in which the halogen atom is in the same ring with the CF_3 group.

The halogenation products of compound VIa are formed as a result of an electrophilic substitution reaction, with the bromination and chlorination processes taking place in different ways. It was found that bromination with excess bromine in trifluoroacetic acid involves substitution exclusively in the 7.8 positions of the free phenylene ring, and as a result, compound VId is formed. In contrast to bromination, chlorination involves both phenylene rings of the 2-trifluoromethyldibenzo-p-dioxine molecule. Passing dry chlorine for 6 h through a boiling solution of compound VIa in acetic acid forms a mixture consisting of 87% of two difficultly separable isomeric dichloro derivatives in the ratio 95:5 with molecular ion masses $[M]^+$ — m/z 320 and 13% of the trichlorosubstituted compound VIa ($[M]^+$ – m/z 354). Longer chlorination did not form any new products.



A study of the physicochemical properties of the above compounds showed that the presence of the CF_3 group in the molecule of halogenated dibenzo-p-dioxine substantially increases their solubility in organic solvents as compared with 2,3,7,8-tetrachlorodibenzo-p-dioxine (Table 3).

Of the synthesized compounds, only compound VId was found to be relatively nontoxic (LD_{50} for white mice of weight > 10 mg/kg). Compounds VIe, f manifest a fairly high toxicity comparable to that of tetrachlorodibenzo-p-dioxine.

To check the purity of the synthesized compounds VIa-f and obtain the mass-spectrometric and chromatographic characteristics, and also to compare them with known polychlorodibenzo-p-dioxines, gas chromatography was combined with mass spectrometry. The principal ions in the mass spectra of the pure compounds VIa-f and their relative retention times and sensitivity coefficients are shown for the tetrachloro derivative, the most toxic xenobiotic (Table 4).

It is well known [9] that $[M]^+$ of unsubstituted dibenzo-p-dioxine has maximum intensity and gives low-intensity (<2%) peaks of the fragment ions $[M\text{-}O]^+$ – m/z 168 and [M-CO]+ – m/z 156. The ions $[M\text{-}2CO]^+$ – m/z 128 (22%) and $[M]^{2+}$ – m/z 92 (14%) are noticeable. As is evident from Table 4, when halogen atoms and the trifluoromethyl group are introduced into the ring, the peak of the molecular ion $[M]^+$ remains maximal as before. The ions $[M\text{-}CO]^+$ and $[M\text{-}1CO]^+$ are observed only in the mass spectrum of compound VIa. After elimination of the halogen and formation of the ions $[M\text{-}R^3]^+$ or $[M\text{-}R^1 \text{ or } (R^2)]^+$ (ion A), ejection of neutral CO particles takes place with formation of $[A\text{-}CO]^+$ (B) and $[B\text{-}CO]^+$ (specifically for compounds VIb-f). A characteristic direction of the decomposition is the splitting off of halogen molecules from the ions $[M]^+$; $[A]^+$; $[B]^+$; $[B\text{-}CO]^+$; $[B\text{-}R^2]^+$, with the successive splitting off all the halogen atoms attached to the aromatic rings. The presence of the trifluoromethyl group in compounds VIa-f is manifested in the specific reaction of detachment of the F atom from the molecular ion $[M]^+$. The peaks of all the fragment ions, including doubly charged ones, have low intensities.

The sensitivity coefficient decreases when 2-trifluoromethyldibenzo-p-dioxine is substituted with chlorine atoms (Table 4), the sensitivity coefficient being practically independent of the number and position of the chlorine atoms. However, when the 2-trifluoromethyl derivative is substituted with two bromine atoms (compound VId), the decrease in sensitivity coefficient is much greater than in the case of substitution with chlorine and bromine atoms, the sensitivity coefficients are the same as for the chlorine-substituted compounds. In retention times, some of these compounds (VIa, c, f) are similar to tetrachlorodibenzo-p-dioxine, and their molecular masses are in the range of the molecular masses of polychlorinated dibenzodioxines with different degrees of chlorination. Thanks to these properties, the synthesized compounds VIa-f can be used as internal standards in sample preparation and in quantitative measurements of polychloro derivatives of dibenzo-p-dioxines.

EXPERIMENTAL

The IR spectra of the compounds in KBr pellets were obtained with a Jasco A-302 spectrophotometer. The PMR spectra were recorded with a WH-90 Bruker spectrophotometer: Operating frequency 90 MHz; solvent, acetone-d_6; internal standard, TMS; temperature, 30°C. The mass spectra were obtained with a Finnigan MAT 8200 chromato-mass-spectrometer under electron impact conditions: ionizing electron energy, 70 eV; cathode emission current, 1 mA; accelerating voltage, 3 kV; 25 m × 0.2 mm quartz capillary column with SE-54 stationary phase; the temperature was programmed from 60°C (holding time, 1 min) to 260°C at a rate of 10°C/min. The course of the reaction and purity of the substances were monitored by GLC on a Chrom-5 chromatograph with a 12 m × 3 mm glass column having a 5% SE-30 stationary phase on Chromaton N-AW-DMCS; carrier gas, N_2; flame ionization detector.

The ultimate analysis data correspond to the calculated data.

General Method of Obtaining the Derivatives VIa-f (Table 2):

A mixture of pyrocatechol, potassium carbonate, and 18-crown-6 in a molar ratio of 1:5:0.1 in 50-100 ml of dry DMFA or absolute acetone is purged with nitrogen and stirred for 1 h at room temperature. To the mixture is added in equimolar amount of o-nitrohalogenated trifluoromethylbenzene relative to pyrocatechol, and the reaction mixture is kept for 6.5 h at the boiling point of the solvent. After cooling, the mixture is poured into 600 ml water with ice, and the precipitate formed is filtered off, washed with water until the reaction of the medium is neutral, and recrystallized.

Bromination of 2-trifluoromethyldibenzo-p-dioxine. To a boiling solution of 2.52 g (0.01 mole) of compound VIa in 50 ml of trifluoroacetic acid is added dropwise with stirring 32.0 g (0.2 mole) of dry bromine. The reaction mixture is boiled for 6 h, cooled to room temperature, and poured into 500 ml of a 10% Na_2SO_3 solution, and the precipitate formed is filtered

TABLE 4. Electron Impact Mass Spectra, Relative Retention Times (RRT), and Relative Sensitivity Coefficients (K) of Compounds VIa-f

Ions, RRT, K	Compound, m/z (I, %)					
	VIa	VIb	VIc	VId	VIe	VIf
	m/z, I	*m/z, I*	*m/z, I*	*m/z, I*	*m/z, I*	*m/z, I*
$[M+6]^+$	—	—	—	—	—	448, 14
$[M+5]^+$	—	—	—	—	—	447, 9
$[M+4]^+$	—	—	324, 10	412, 50	358, 31	446, 69
$[M+3]^+$	—	—	323, 8	411, 14	357, 13	445, 14
$[M+2]^+$	—	288, 30	322, 64	410, 100	356, 94	444, 100
$[M+1]^+$	253, 14	287, 13	321, 13	469, 7	355, 14	443, 7
$[M]^+$	252, 100	286, 100	320, 100	408, 51	354, 100	442, 43
$[M-F]^+$	233, 5	267, 4	301, 4	391, 4 389, 2	337, 3 335, 3	425, 4 423, 2
$[M-R^3]^+ [A]^+$	—	251, 5	—	—	—	409, 4 407, 3
$[M-R^1]^+ [A]^+$	—	—	285, 3	331, 4 329, 4	321, 3 319, 6	365, 5 363, 3
$[M-CO]^+$	224, 3	—	—	—	—	—
$[M-2CO]^+$	196, 4	—	—	—	—	—
$[A-CO]+[B]^+$	—	223, 6	259, 7 257, 22	303, 8 301, 8	293, 13 291, 22	337, 8 335, 6
$[B{\cdot}CO]^+$	—	195, 8	229, 5	275, 3 273, 3	265, 3 263, 4	309, 3 307, 2
$[B-R^2]^+$	—	—	222, 3	222, 2	256, 3	—
$[A-R^2]^+$	—	—	—	—	—	286, 8 284, 25
$[(B{\cdot}CO)-HF]^+$	—	175, 5	209, 3	—	—	—
$[(A-R^2)-R^3]^+$	—	—	—	—	—	249, 4
$[(B-CO)-R^2]+[C]^+$	—	—	194, 5	194, 12	228, 5	230, 3 228, 8
$[C-R^3]^+$	—	—	—	—	193, 6	193, 10
$[M+4]^{2+}$	—	—	—	206, 3	179, 2	223, 4
$[M+2]^{2+}$	—	—	161, 3	205, 5	178, 6	222, 7
$[M]^{2+}$	126, 2	143, 5	160, 6	204, 3	177, 5	221, 3
RRT	0,528	0.665	0,765	0,883	0,889	1,005
K	1,72	1,28	1,25	0,71	1,25	1,27

off, washed with water, dried, and successively recrystallized from 85% and 50% acetic acid with activated carbon. There is obtained 3.2 g (64%) of a white crystalline substance with mp. 88-100°C. A mixing test with the substance obtained by the general method did not produce a lowering of the melting point.

Chlorination of 2-trifluoromethyldibenzo-p-dioxines. Through a boiling solution of 1.9 g (9.5 mmole) of compound VIa in 40 ml of glacial acetic acid dry chlorine is passed for 6 h. The reaction mixture is poured into 500 ml of water, and the precipitate is filtered off, washed with water to a neutral reaction, and dried in air. There is obtained 2.0 g of a white crystalline substance containing 87% of a mixture of dichlorinated derivatives of compound VIa in the ratio of 95:5 and 13% of the trichlorosubstituted product VIa.

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