SYNTHESIS OF 7-CHLORO-2-BENZOFURYL ARYL KETONES

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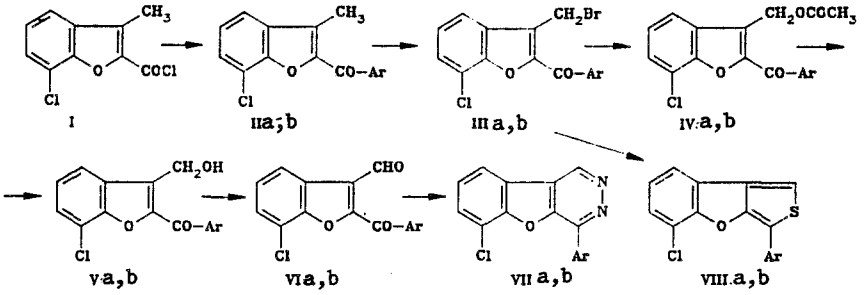
7-Chloro-3-methyl-2-benzofuryl aryl ketones and a number of their derivatives were obtained by the Friedel–Crafts reaction from 7-chloro-3-methylbenzofurancarboxylic acid chloride and benzene or anisole.

We have previously described a method for obtaining formyl derivatives of benzofuran [1, 2]. The present research is devoted to the synthesis of previously undescribed aryl benzofuryl ketones. The starting 7-chloro-3-methylbenzofurancarboxylic acid chloride (I), which was obtained by the method in [3], was subjected to the Friedel–Crafts reaction with benzene and anisole, and 7-chloro-3-methyl-2-benzofuryl aryl ketones IIa, b were obtained. These compounds on bromination at the methyl group with N-bromosuccinimide give 7-chloro-3-bromomethyl-2-benzofuryl ketones IIIa, b, which were converted to 3-acetoxymethyl derivatives IVa, b. The hydrolysis of IVa, b led to 7-chloro-3-hydroxymethylbenzofuryl ketones Va, b, the oxidation of which by means of pyridine dichromate [4] gives 7-chloro-3-formylbenzofuryl ketones VIa, b. The reaction of aldehydes VIa, b with hydrazine hydrate leads to condensed 6-chlorobenzofuryl[2,3,-d]pyridazines VIIa, b. In addition, 5-chlorothieno-[3,4-b]benzofurans VIIIa, b were obtained starting from IIIa, b.



II—VIII a Ar = C_6H_5, b Ar = $C_6H_4OCH_3$-*p*

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla B-487 spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

The characteristics of II-VIII are presented in Table 1.

7-Chloro-3-methyl-2-benzofuryl Phenyl Ketone (IIa). A mixture of 4.6 g (20 mmoles) of furancarboxylic acid chloride I, 2.7 g (20 mmoles) of anhydrous $AlCl_3$, and 20 ml of benzene was refluxed with stirring for 5 h, after which it was cooled, and the resulting complex was decomposed by adding 25 ml of water and 2 ml of 5% HCl. The organic layer was separated, washed successively with two 25-ml portions of 10% $NaHCO_3$ solution and three 20-ml portions of water, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo, and the residue was crystallized from hexane. 7-Chloro-3-methyl-2-benzofuryl methoxyphenyl ketone (IIb) was similarly obtained starting from anisole.

3-Bromomethyl-7-chloro-2-benzofuryl Phenyl Ketone (IIIa). A mixture of 2.7 g (10 mmoles) of IIa, 1.8 g (10 mmoles) of N-bromosuccinimide, 0.1 g of benzoyl peroxide, and 50 ml of CCl_4 was refluxed for 4 h. The precipitate was removed by filtration, the filtrate was evaporated in vacuo, and the product was crystallized from heptane. 3-Bromomethyl-7-chloro-2-benzofuryl methoxyphenyl ketone (IIIb) was similarly obtained.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	PMR spectrum, ppm ($CDCl_3$) (without the protons of the benzene ring)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	Cl		C	H	Cl	
IIa	102...103	2,60 (3H, s, CH_3)	70,1	4,1	13,1	$C_{16}H_{11}ClO_2$	70,1	4,0	13,0	66
IIb	91...92	2,60 (3H, s, CH_3), 3,85 (3H, s, OCH_3)	67,9	4,3	11,8	$C_{17}H_{13}ClO_3$	67,8	4,2	11,9	70
IIIa	138...139	5,10 (2H, s, CH_2)	55,0	2,9	—	$C_{16}H_{10}BrClO_2$	55,1	2,9	—	74
IIIb	106...107	3,85 (3H, s, OCH_3), 5,10 (2H, s, CH_2)	53,8	3,2	—	$C_{17}H_{12}BrClO_3$	53,9	3,3	—	73
IVa	105...106	2,10 (3H, s, CH_3), 5,50 (2H, s, CH_2O)	65,8	4,0	10,8	$C_{18}H_{13}ClO_4$	65,7	4,1	10,7	96
IVb	79...80	2,20 (3H, s, CH_3), 3,80 (3H, s, OCH_3), 5,40 (2H, s, CH_2O)	63,6	4,2	9,9	$C_{19}H_{15}ClO_5$	63,7	4,2	10,0	90
Va	114...115	3,70 (1H, s, OH), 5,05 (2H, s, CH_2)	67,0	3,8	12,4	$C_{16}H_{11}ClO_3$	67,1	3,9	12,5	97
Vb	82...83	3,65 (1H, s, OH), 3,85 (3H, s, OCH_3), 5,10 (2H, s, CH_2)	64,5	4,1	11,2	$C_{17}H_{13}ClO_4$	64,4	4,2	11,1	93
VIa	132...133	10,50 (1H, s, CHO)	64,0	3,2	12,5	$C_{16}H_9ClO_3$	64,1	3,1	12,6	76
VIb	98...99	3,85 (3H, s, OCH_3), 10,45 (1H, s, CHO)	64,9	3,5	11,3	$C_{17}H_{11}ClO_4$	65,0	3,4	11,2	68
VIIa	224...225	8,40...7,80 (4H, m, arom.), 7,60...7,20 (5H, m, arom.)	68,5	3,2	10,0	$C_{16}H_9ClN_2O$	68,6		9,9	72
VIIb	211...213	3,85 (3H, s, OCH_3), 7,20...7,55 (4H, m, arom.) 7,75...8,40 (4H, m, arom.)	65,7	3,5	9,0	$C_{17}H_{11}ClN_2O_2$	65,8	3,6	9,1	67
VIIIa	79...80	7,20...8,25 (9H, m, arom.)	67,5	3,2	12,5	$C_{16}H_9ClOS$	67,6	3,1	12,6	72
VIIIb	106...107	3,90 (3H, s, OCH_3), 7,25...8,30 (8H, m, arom.)	64,9	3,4	11,5	$C_{17}H_{11}ClO_2S$	64,8	3,4	11,4	74

3-Acetoxymethyl-7-chloro-2-benzofuryl Phenyl Ketone (IVa). A mixture of 2 g (5.7 mmoles) of IIIa and 2 g (20 mmoles) of CH_3COOK in 40 ml of acetic acid was heated for 6 h, after which the mixture was concentrated, and 50 ml of water was added to it. The product was extracted with chloroform, and the extract was washed with two 25-ml portions of 10% Na_2CO_3 solution and water, dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the product was crystallized from heptane. 3-Acetoxymethyl-7-chloro-2-benzofuryl methoxyphenyl ketone (IVb) was similarly obtained.

7-Chloro-3-hydroxymethyl-2-benzofuryl Phenyl Ketone (Va). A solution of 1.3 g (3.9 mmoles) of IVa in 50 ml of absolute ethanol and 1 ml of sulfuric acid was allowed to stand for 24 h at 20°C, after which the mixture was concentrated to a volume of 10 ml, and the resulting precipitate was extracted with four 20-ml portions of chloroform. The chloroform was removed by distillation, and the product was crystallized from hexane. 7-Chloro-3-hydroxymethyl-2-benzofuryl methoxyphenyl ketone (Vb) was similarly obtained.

7-Chloro-3-formyl-2-benzofuryl Phenyl Ketone (VIa). A 1.2-g (5.6 mmoles) sample of pyridine dichromate was added in small portions to a mixture of 0.8 g (2.8 mmoles) of Va in 15 ml of methylene chloride, and the resulting mixture was stirred for 6 h at room temperature. Ether (50 ml) was then added, and the mixture was filtered. The filtrate was passed through a column packed with silica gel and evaporated, and the product was crystallized from hexane. 7-Chloro-3-formyl-2-benzofuryl methoxyphenyl ketone (VIb) was similarly obtained.

6-Chloro-4-phenylbenzofuro[2,3-d]pyridazine (VIIa). A solution of 285 mg (1 mmole) of VIa, 100 mg (2 mmoles) of hydrazine hydrate, and 20 ml of ethanol was refluxed for 4 h, after which the solvent was evaporated, and the residue was crystallized from ethyl acetate. 6-Chloro-4-methoxyphenylbenzofuro[2,3-d]pyridazine (VIIb) was similarly obtained.

5-Chloro-3-phenylthieno[3,4-b]benzofuran (VIIIa). A mixture of 520 mg (1.5 mmoles) of IIIa, 100 mg (1.5 mmoles) of thioacetamide, and 10 ml of ethanol was refluxed with stirring for 6 h, after which the solvent was evaporated, and the residue was crystallized from ethanol. 5-Chloro-3-methoxyphenylthieno[3,4-b]benzofuran (VIIIb) was similarly obtained.

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