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SYNTHESIS OF AROYLBENZOFURANS

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Materials possessing coronary dilation [1, 5], anesthetic [3], and spasmolytic [1] properties are found among the acylated derivatives of benzofurans. The discovery of compounds possessing antiviral effects among the bis-benzofuranyl ketones also has been communicated [4]. Further, the aroylbenzofurans are convenient starting compounds for the synthesis of benzofuranylarylcarbinols showing hypocholesterolemic action [7] and are useful for treatment of cardiovascular disease [6]. Taking into account the above, we continued to investigate the synthesis of new derivatives of benzofuranyl ketones with the aim of studying their pharmacological activity.

Condensation of 2-methyl-3-bromoacetyl-5-methoxybenzofuran [2] with salicylaldehyde or its 5-methoxy-, 5-bromo-, or 5-nitro-derivative gave a series of 2-methyl-5-methoxybenzofurans containing a 2'-benzoylfuroyl group in position 3. This enabled the preparation of 3-(benzofuroyl-2')-(I), 3-(5'-methoxybenzofuroyl-2')-(II), 3-(5'-bromobenzofuroyl-2')-(III), and 2-methyl-3-(5'-nitrobenzofuroyl-2')-5-methoxybenzofuran (IV).

Compounds I-IV were successfully reduced with $NaBH_4$ to the corresponding carbinols VI-VIII in yields of 71-86%. In experiments to synthesize hydroxy group derivatives of IV-VIII such as aminoalkyl esters of carbamates, we obtained either the starting materials or polymers. Experiments to demethylate compounds I-IV with the help of HBr or $AlCl_3$ also were unsuccessful. To obtain 2-methyl-3-(5'-R-benzofuroyl-2')-5-hydroxybenzofurans and its derivatives we used salicylaldehyde and its derivatives, and instead of 5-methoxy-2-methyl-3-bromoacetylbenzofuran, the corresponding 5-acetoxybenzofuran (IX). The latter was prepared by bromination of 2-methyl-3-acetyl-5-acetoxybenzofuran with dioxane dibromide. The products of condensation of compound IX with salicylaldehyde and its derivatives were the 2-methyl-3-(5'-R-benzofuroyl-2')-5-acetoxybenzofurans which were deacylated without isolation by boiling in the presence of concentrated HCl. These paths synthesized 3-(benzofuroyl-2')-(X), 3-(5'-methoxybenzofuroyl-2')-(XI); 3-(5'-bromobenzofuroyl-2')-(XII); and 2-methyl-3'-(5'-nitrobenzofuroyl-2')-5-hydroxybenzofuran (XIII).

Aminomethylation of compounds X-XIII by the action of bis-dimethylaminomethane gave the corresponding 4-dimethylaminomethyl derivatives (XIV-XVII).

The method that we used for the synthesis of 3-benzofuroylbenzofurans was applied to prepare other 3-heteroyl derivatives such as 2-methyl-3-(4',5'-diphenylthenoyl-2')-5-methoxybenzofuran (XVIII). The compound was obtained in 60.9% yield by boiling 2-methyl-3-bromoacetyl-5-methoxybenzofuran with 1,2-diphenyl-2-mercaptoacrolein in the presence of K_2CO_3.

On the basis of the 3-bromoacetyl derivative we also synthesized 3-(imidazol-1-ylacetyl)-XIX and 2-methyl-3-isopropylaminoacetyl-5-methoxybenzofuran, characterized as the hydrochloride (XX)(cf. Table 1).

The interaction of 2-bromomethyl-3-carboethoxy-5-methoxybenzofuran with imidazole gave 2-(imidazol-1-ylmethyl)-3-carboethoxy-5-methoxybenzofuran (XXI) in 75% yield.

The synthesized compounds XIV-XVI and XVIII-XX were surveyed for their pharmacological activity in the Pharmacological Laboratory, and compounds XIX and XXI for their antibacterial

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TABLE 1. Characteristics of Compounds I-XX

Compound	Yield,%	mp, °C (solvent)	M+	Empirical formula
I	80,1	82—3 (EA-hexane)	306	$C_{19}H_{14}O_4$
II	84	108—9 (EA-heptane)	336	$C_{20}H_{16}O_5$
III	72,7	147—8 (EA)	384	$C_{19}H_{13}BrO_4$
IV	26,3	191—3 (EA)	351	$C_{19}H_{13}NO_6$
V	74,7	109 (EA-heptane)	308	$C_{19}H_{16}O_4$
VI	71	137—8 (MeOH)	338	$C_{20}H_{18}O_5$
VII	86,3	128—9 (MeOH)		$C_{19}H_{15}BrO_4$
VIII	71,7	163—5 (EtOH)	353	$C_{19}H_{15}NO_6$
IX	82,8	100—1 (MeOH)		$C_{13}H_{11}BrO_4$
X	77	141—3 (MeOH)	292	$C_{18}H_{12}O_4$
XI	96	190 (EA)		$C_{19}H_{14}O_5$
XII	71,4	230—3 (AcoH)		$C_{18}H_{11}BrO_4$
XIII	85,7	206—8	337	$C_{18}H_{11}NO_6$
XIV	59,6	105—7 (MeOH)	349	$C_{21}H_{19}NO_4$
Hydrochloride of XIV	73,3	192—4 (Ac — MeOH — ether)		$C_{21}H_{19}NO_4 \cdot HCl \cdot H_2O$
XV	65,6	110 (MeOH)		$C_{22}H_{21}NO_5$
Hydrochloride of XV	98	202—5 (Ac — MeOH — ether)		$C_{22}H_{21}NO_5 \cdot HCl$
XVI	68,8	150—60 (MeOH)		$C_{21}H_{18}BrNO_4$
Hydrochloride of XVI		177 (Ac — MeOH — ether)		$C_{21}H_{18}BrNO_4 \cdot HCl \cdot H_2O$
XVII		173—6		$C_{21}H_{18}BrNO_4 \cdot HCl \cdot H_2O$
Hydrochloride of XVII	43,6	216—17 (Ac — MeOH — ether)		$C_{21}H_{18}N_2O_6 \cdot HCl$
XVIII	60,9	146—7	424	$C_{27}H_{20}O_3S$
XIX	70	118—29 (EA)		$C_{15}H_{14}N_2O_3$
Hydrochloride of XX	37	175—82		$C_{15}H_{19}NO_3 \cdot HCl$

Note. EA) ethyl acetate; Ac) acetone; R^I) H(I-XIII, XVIII-XX, hydrochloride of XX), CH_2NMe_2(XIV-XVII and hydrochlorides); R^{II}) H(X-XVII, hydrochlorides of XIV-XVII), CH_3 (I-VIII, XVIII-XX, hydrochloride of XX), Ac(IX).

activity in the Chemotherapeutic Laboratory of Infectious Diseases of the All-Union Scientific Research Institute of Pharmaceutical Chemistry.

The results of these studies showed that compounds XIV, XVI, XVIII, and XIX were of low toxicity ($LD_{50} \geq 500$ mg/kg), and compound XV was moderately toxic ($LD_{50} = 200$ mg/kg, internal).

For studies of the analgetic and anti-inflammatory activity of these materials, it was established that at doses corresponding to 10% of the LD_{50}, compounds XIV-XVI, XVIII and XIX did not exhibit antiexudative activity. Compounds XV, XVI, and XIX, however, showed a nonsignificant decrease (by 20-25%) in animals in the amount of "writhing" reaction to the disease. The indicated compounds showed a weaker analgetic activity than acetylsalicylic acid. Compounds XIV and XVIII did not possess analgetic properties.

The local anesthetic activity was studied with compounds XVI and XIX. It was found that for compound XVI the Ren index for surface anesthesia in rabbit eye cornea (0.05% solution) was 472 ± 130, significantly exceeding lidocaine, and comparable in activity to marcaine. Compound XIX did not show local anesthetic activity.

Compound XXI showed weak antituberculin and antibacterial activity.

EXPERIMENTAL

The characteristics of the synthesized compounds are presented in Table 1.

The values found for the elemental analyses corresponded with those calculated.

2-Methyl-3-(benzofuroyl-2')-5-methoxybenzofuran (I). To a solution of 8 g (0.065 mole) of salicylaldehyde in 180 ml of acetone was added 18.1 g (0.131 mole) of K_2CO_3, and then 18.6 g (0.065 mole) of 2-methyl-3-bromoacetyl-5-methoxybenzofuran and the reaction mixture was boiled with stirring for 5 h. The precipitate was separated and the acetone was distilled. The residue was recrystallized from a mixture of ethyl acetate and hexane.

2-Methyl-3-(5'-methoxybenzofuroyl-2')-5-methoxybenzofuran (II), 2-methyl-3-(5'-bromobenzofuroyl-2')-5-methoxybenzofuran (III), and 2-methyl-3-(5'-nitrobenzofuroyl-2')-5-methoxybenzofuran (IV) were prepared analogously to compound I.

(2-Methyl-5-methoxybenzofuryl-3)-(benzofuryl-2') carbinol (V). To a solution of 3.06 g (0.01 mole) of compound I in 25 ml of dioxane heated to a temperature of 40-50°C was added dropwise a solution of 0.37 g (0.01 mole) of $NaBH_4$ in 3 ml of H_2O. The reaction mixture was boiled for 2 h, cooled, and neutralized with 30 ml of $(NH_4)_2SO_4$. After diluting with water

and stirring for 2 h, the precipitate was separated, dried, and recrystallized from a mixture of ethyl acetate and pentane.

(2-Methyl-5-methoxybenzofuryl-3)-(5'-methoxybenzofuryl-2')carbinol (VI), (2-methyl-5-methoxybenzofuryl-3)-(5'-bromobenzofuryl-2') carbinol (VII), and (2-methyl-5-methoxybenzofuryl-3)-(5'-nitrobenzofuryl-2')carbinol (VIII) were prepared analogously to compound V.

2-Methyl-3-bromoacetyl-5-acetoxybenzofuran (IX). To a solution of 23.2 g (0.1 mole) of 2-methyl-3-acetyl-5-acetoxybenzofuran in 130 ml of dioxane at room temperature by adding dropwise over 1 h a solution of 16 g (0.1 mole) of bromine in 100 ml of dioxane. The reaction mixture was stirred for 3 h, poured into water and the resulting precipitate was isolated.

2-Methyl-3-(benzofuroyl-2')-5-hydroxybenzofuran (X). To a solution of 2.44 g (0.02 mole) of salicylaldehyde in 60 ml of acetone was added 5.52 g (0.04 mole) of K_2CO_3, and then 6.22 g (0.02 mole) of compound IX and the reaction mixture was stirred and boiled for 5 h. The precipitate was separated and the acetone was removed. The residue was dissolved in 60 ml of MeOH and boiled with 20 ml of concentrated HCl for 1 h. The reaction mixture was cooled, added to water, and the precipitate was separated. The product was purified from resins by chromatography on a silica gel column (ether) and recrystallized from MeOH.

2-Methyl-3-(5'-methoxybenzofuroyl-2')-5-hydroxybenzofuran (XI), 2-methyl-3-(5'-bromobenzofuroyl-2')-5-hydroxybenzofuran (XII), and 2-methyl-3-(5'-nitrobenzofuroyl-2')-5-hydroxybenzofuran (XIII) were prepared analogously to compound X.

2-Methyl-3-(benzofuroyl-2')-4-dimethylaminomethyl-5-hydroxybenzofuran Hydrochloride Monohydrate (XIV). A mixture of 3.65 g (0.0125 mole) of compound X and 4 ml of bis-dimethylaminomethane in 40 ml of dioxane was boiled for 3 h. The solvent and excess amine were distilled. The residue was purified from resin by chromatography on an alumina column (ether).

The hydrochloride was obtained by neutralization of the base with ethereal HCl.

2-Methyl-3-(5'-methoxybenzofuroyl-2')-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride (XV), 2-methyl-3-(5'-bromobenzofuroyl)2')-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride monohydrate (XVI), and 2-methyl-3-(5'-nitrobenzofuroyl-2')-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride (XVII) were obtained by a route analogous to that of compound XIV.

2-Methyl-3-(4',5'-diphenylthenoyl-2')-5-methoxybenzofuran (XVIII) was prepared analogously to compound I from 1,2-diphenyl-2-mercaptoacrolein and 2-methyl-3-bromoacetyl-5-methoxybenzofuran.

2-Methyl-3-(imidazol-1-ylacetyl)-5-methoxybenzofuran (XIX). A solution of 5.66 g (0.02 mole) of 2-methyl-3-bromoacetyl-5-methyoxybenzofuran in 150 ml of acetone and 13.6 g (0.2 mole) of imidazole in the presence of 5 g of $NaHCO_3$ was boiled for 3 h. The precipitate was removed and the acetone was distilled. The residue after washing from excess imidazole with water was chromatographed in ethyl acetate on a silica gel column.

2-Methyl-3-isopropylaminoacetyl-5-methoxybenzofuran Hydrochloride (XX). A solution of 5.66 g (0.02 mole) of 2-methyl-3-bromoacetyl-5-methoxybenzofuran in 60 ml of benzene and 2.95 g (0.05 mole) of i-$PrNH_2$ was kept at room temperature for 2 days. The precipitate was removed and the benzene was distilled. The residue was chromatographed in ether on an Al_2O_3 column. The hydrochloride of XX was obtained by neutralization of the base with ethereal HCl.

2-(Imidazol-1-ylmethyl)-3-carbethoxy-5-methoxybenzofuran (XXI) was obtained in a fashion analogous to that of compound XIX ((boiling time = 14 h); yield = 75%, mp = 111-112°C (from ethyl acetate)). M^+ 300. $C_{16}H_{16}N_2O_4$.

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