2-BROMOMETHYL DERIVATIVES OF BENZOFURAN AND INDOLE AND THEIR REACTIONS WITH SOME NUCLEOPHILIC REAGENTS

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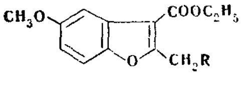
UDC 547.728.1'756 : 542.944.1

The corresponding 2-bromomethyl derivatives of benzofuran and indole were obtained by bromination of 2-methyl-3-carbethoxy-5-methoxybenzofuran and 1,2-dimethyl-3-carbethoxy-5-methoxyindole with N-bromosuccinimide. A number of alkyl(aryl)thiomethyl and dialkylaminomethyl derivatives were obtained by reaction of the 2-bromomethyl derivatives with nucleophilic reagents.

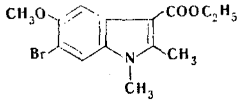
We have previously obtained biologically active 2-alkyl(aryl)thiomethyl-5-hydroxyindole derivatives in low yield via the Nenitzescu reaction starting from enamines of γ-alkyl(aryl)mercaptoacetoacetic ester and p-benzoquinones [1].

We have studied the bromination of 5-methoxybenzofuran and 5-methoxyindole derivatives with N-bromosuccinimide in nonaqueous solvents via the method in [2-4]. We obtained 2-bromomethyl-3-carbethoxy-5-methoxybenzofuran (II) by bromination of 2-methyl-3-carbethoxy-5-methoxybenzofuran (I) with N-bromosuccinimide in the presence of benzoyl peroxide and illumination. Only 1,2-dimethyl-3-carbethoxy-5-methoxy-6-bromoindole (IV) is formed under similar conditions in the reaction of N-bromosuccinimide with 1,2-dimethyl-3-carbethoxy-5-methoxyindole (III).

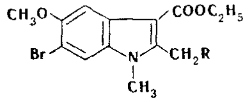
The aromatic 6-H and 7-H protons in the PMR spectrum of II give two doublets (δ 6.80 and 7.0 ppm) and a singlet (7.42 ppm), and the singlet has an additional splitting. The signal of the protons of a 2-CH_3 group is absent at 2.6 ppm, but there is a signal of protons of a CH_2Br group at 4.92 ppm (singlet). Structure IV is confirmed by the presence of signals at 7.26 ppm in the form of a split singlet and at 2.60 ppm, which are affiliated, respectively, with the aromatic 4-H and 7-H protons and the protons of the 2-CH_3 group. This result is also in agreement with the data obtained in the bromination of a 5-hydroxyindole derivative with bromine in acetic acid [5].



II, VI-XVII



IV



V, XVIII-XXIII

II, V R = Br–; VI, XIX R = p-$CH_3C_6H_4S$–; VII, XVIII R = C_6H_5S–; VIII, XX R = $C_6H_5CH_2S$–;

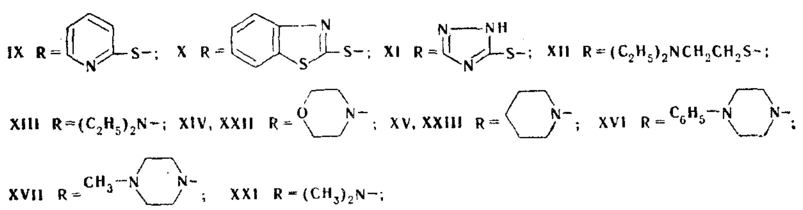


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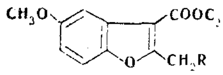
TABLE 1. 5-Methoxybenzofuran Derivatives



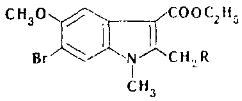
Compound	mp, °C[a]	R_f	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
VII	49—50	0,80	66,7	5,3	—	$C_{19}H_{18}O_4S$	66,6	5,3	—	94
VIII	66—67	0,71	67,2	5,7	—	$C_{20}H_{20}O_4S$	67,4	5,6	—	97
IX	61—62	0,58	62,6	5,1	4,0	$C_{18}H_{17}NO_4S$	62,9	5,0	4,1	94
X	92—93	0,70	59,9	4,3	3,4	$C_{20}H_{17}NO_4S_2$	60,1	4,3	3,5	57
XI	125—126	—	54,2	4,5	12,3	$C_{15}H_{15}N_3O_4S$	54,0	4,5	12,4	90
XII	114[b]	0,52[c]	56,7	7,1	3,2	$C_{19}H_{28}ClNO_4S$	56,7	7,0	3,5	Quantitative
XIV	91—92	0,14	63,8	6,8	4,1	$C_{17}H_{21}NO_5$	63,9	6,6	4,4	78
XV	198—200[b]	0,30	61,0	6,8	3,8	$C_{18}H_{24}ClNO_4$	61,1	6,8	3,9	79

[a] Compound VII was recrystallized from petroleum ether; VIII, X, XI, and XIV were recrystallized from alcohol; and IX was recrystallized from heptane—absolute alcohol.

[b] This is the melting point of the hydrochloride.

[c] In chloroform.

TABLE 5. 5-Methoxyindole Derivatives



Compound	mp, °C[a]	R_f	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
XIX	113—114	0,61	56,1	4,9	3,0	$C_{21}H_{22}BrNO_3S$	56,2	5,0	3,1	89
XX	144—145	0,62	56,1	5,1	3,1	$C_{21}H_{22}BrNO_3S$	56,2	5,0	3,1	90
XXII	142—143	0,21	52,6	5,7	6,8	$C_{18}H_{23}BrN_2O_4$	52,6	5,6	6,8	93
XXIII	124—125	0,61	55,7	6,2	7,0	$C_{19}H_{25}BrN_2O_3$	55,7	6,2	6,9	83

[a] Compound XIX was recrystallized from absolute alcohol, XX was recrystallized from absolute alcohol—benzene, XXII was recrystallized from alcohol, and XXIII was recrystallized from heptane.

We obtained 1-methyl-2-bromomethyl-3-carbethoxy-5-methoxy-6-bromoindole (V) by bromination of IV with N-bromosuccinimide in the presence of benzoyl peroxide with illumination. Two singlet signals at 6.73 and 6.82 ppm, which are affiliated with the para 4-H and 7-H protons, are observed in the PMR spectrum of V. The disappearance of the signal of protons of a 2-CH_3 group at 2.6 ppm and the appearance of a signal of protons of a CH_2Br group at 5.04 ppm (singlet) are evidence for bromination in the side chain.

The products of bromination of II and V readily react with nucleophilic reagents — mercaptans, thiophenols, and secondary amines — to give 2-alkyl(aryl)thiomethyl and 2-dialkylaminomethyl derivatives of benzofuran (VI-XVII) and indole (XVIII-XXIII) in 70-90% yields. Thin-layer chromatography was used to evaluate the individualities of the compounds obtained.

EXPERIMENTAL

The PMR spectra of deuterochloroform solutions of the compounds were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. Thin-layer chromatography was carried out on a loose layer of activity-II aluminum oxide in benzene.

2-Bromomethyl-3-carbethoxy-5-methoxybenzofuran (II). A mixture of 6.5 g (27 mmole) of I, 5.7 g (32 mmole) of N-bromosuccinimide,* and 0.27 g of benzoyl peroxide in 100 ml of dry CCl_4 was refluxed for 6 h with illumination with a 300-W lamp at a distance of 10 cm from the reaction flask. The precipitated succinimide was removed by filtration and washed with CCl_4. The filtrate was evaporated in vacuo to

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*The N-bromosuccinimide was recrystallized from water and dried in vacuo (1-2 mm) over phosphorus pentoxide for 4 h.

give 6.25 g (71%) of a product with mp 80-81° (from alcohol) and R_f 0.83. Found: C 49.8; H 4.3; Br 25.0%. $C_{13}H_{13}BrO_4$. Calculated: C 49.9; H 4.2; Br 25.5%.

1,2-Dimethyl-3-carbethoxy-5-methoxy-6-bromoindole (IV). A mixture of 6.2 g (25 mmole) of III, 4.4 g (25 mmole) of N-bromosuccinimide, 0.25 g of benzoyl peroxide, and 80 ml of dry CCl_4 was treated under the same conditions as in the synthesis of II to give 6.4 g (80%) of a product with mp 164-165° (from CCl_4) and R_f 0.5. Found: C 51.5; H 4.8; Br 24.6; N 4.4%. $C_{14}H_{16}BrNO_3$. Calculated: C 51.6; H 5.0; Br 24.5; N 4.4%.

1-Methyl-2-bromomethyl-3-carbethoxy-5-methoxy-6-bromoindole (V). A 1.6-g (9 mmole) sample of N-bromosuccinimide was added in the course of 1 h with illumination with a 300-W lamp to a refluxing solution of 3.26 g (10 mmole) of IV and 0.01 g of benzoyl peroxide in 40 ml of dry CCl_4. The mixture was refluxed for another 5 h, after which the succinimide was removed by filtration and washed with CCl_4. The filtrate was cooled, and the resulting precipitate was removed by filtration to give 3.35 g (90%) of a product with mp 141-142° (from CCl_4) and R_f 0.63. Found: C 40.9; H 3.9; Br 39.8; N 3.4%. $C_{14}H_{15}Br_2NO_4$. Calculated: C 41.5; H 3.7; Br 39.4; N 3.5%.

2-(p-Tolylthio)methyl-3-carbethoxy-5-methoxybenzofuran (VI). A 0.37-g (3 mmole) sample of p-thiocresol and a solution of 0.94 g (3 mmole) of II in 10 ml of absolute alcohol were added successively with stirring to a solution of 0.17 g (3 mmole) of KOH in 10 ml of absolute alcohol. After 3 h, the reaction solution was diluted with water, and the precipitate was removed by filtration and dried to give 1 g (93.5%) of a compound with mp 51° (from alcohol) and R_f 0.72. Found: C 66.9; H 5.6; S 9.1%. $C_{20}H_{20}O_4S$. Calculated: C 67.4; H 5.6; S 9.0%.

Compounds VII-XII were similarly obtained (Table 1).

2-Diethylaminomethyl-3-carbethoxy-5-methoxybenzofuran (XIII) Hydrochloride. A 1.5-g (20 mmole) sample of diethylamine was added to a solution of 3.1 g (10 mmole) of II in 30 ml of benzene. The next day, the precipitated diethylamine hydrobromide was removed by filtration, and a solution of dry hydrogen chloride in absolute alcohol was added to the filtrate to give 2.9 g (85.3%) of a product with mp 137-138° (from acetone–ether) and R_f 0.34. Found: C 59.9; H 7.3; N 4.1%. $C_{17}H_{23}NO_4 \cdot HCl$. Calculated: C 59.7; H 7.1; N 4.1%.

Compounds XIV-XV (Table 1) were similarly obtained.

2-(4'-Phenylpiperazinomethyl)-3-carbethoxy-5-methoxybenzofuran (XVI). A solution of 3.1 g (10 mmole) of II in 20 ml of benzene was added to a mixture of 1.6 g (10 mmole) of N-phenylpiperazine and 3 g of triethylamine in 10 ml of benzene. The next day, the precipitated triethylamine hydrobromide was removed by filtration, and the filtrate was vacuum-evaporated to dryness. The residue was washed with water and alcohol and dried to give 2.6 g (66%) of a product with mp 117° (from alcohol) and R_f 0.30. Found: C 69.9; H 6.6; N 6.8%. $C_{23}H_{26}N_2O_4$. Calculated: C 70.0; H 6.7; N 7.1%.

2-(4'-Methylpiperazinomethyl)-3-carbethoxy-5-methoxybenzofuran (XVII) Hydrochloride. Similarly, 2.8 g (70%) of the dihydrochloride with mp 226-227° (from methanol–ether) and R_f 0.11 was obtained from 1 g (10 mmole) of N-methylpiperazine, 3.1 g (10 mmole) of II and 3 g of triethylamine. Found: C 53.3; H 6.5; N 6.9%. $C_{18}H_{24}N_2O_4 \cdot 2HCl$. Calculated: C 53.1; H 6.5; N 6.9%.

1-Methyl-2-phenylthiomethyl-3-carbethoxy-5-methoxy-6-bromoindole (XVIII). A 0.55-g (5 mmole) sample of thiophenol and a solution of 2 g (5 mmole) of V in 25 ml of benzene were added successively with stirring to a solution of 0.28 g (0.005 mole) of KOH in 5 ml of alcohol. The next day, the potassium bromide was removed by filtration, the filtrate was vacuum-evaporated, and the residue was washed with water and alcohol to give 1.9 g (87.5%) of a product with mp 129-130° (from absolute alcohol) and R_f 0.6. Found: C 54.9; H 4.7; N 3.3%. $C_{20}H_{20}BrNO_3S$. Calculated: C 55.3; H 4.6; N 3.2%.

Compounds XIX and XX (Table 2) were similarly obtained.

1-Methyl-2-dimethylaminomethyl-3-carbethoxy-5-methoxy-6-bromoindole (XXI). A solution of 0.45 g (10 mmole) of dimethylamine in absolute alcohol was added to a solution of 2 g (5 mmole) of V in 25 ml of benzene. The next day, the precipitated dimethylamine hydrobromide was removed by filtration, the filtrate was vacuum-evaporated to dryness, and the residue was washed with alcohol to give 1.5 g (81%) of a product with mp 116-117° (from absolute alcohol) and R_f 0.37. PMR spectrum (CCl_4, hexamethyldisiloxane internal standard), ppm: 7.31; 7.50 (singlet, 4-H, 7-H); 2.8 [$N(CH_3)_2$]. Found: C 52.3; H 5.5; N 7.7%. $C_{16}H_{21}BrN_2O_3$. Calculated: C 52.0; H 5.7; N 7.6%.

Compounds XXII and XXIII were similarly obtained.

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