VILSMEIER FORMYLATION OF 2-METHYL-3-CARBETHOXY-5-METHOXY- AND 2-METHYL-5-METHOXYINDOLES

V. I. Shvedov, A. K. Chizhov, and A. N. Grinev

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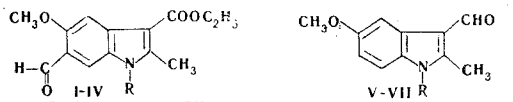
The corresponding 6- and 3-formyl derivatives were obtained by formylation of 2-methyl-3-carbethoxy-5-methoxy- and 2-methyl-5-methoxyindole derivatives.

For the first time we have studied the formylation of 2-methyl-3-carbethoxy-5-methoxyindole derivatives. As a result of the reaction we obtained 6-formyl derivatives I-IV. The structures of these compounds were confirmed by the PMR spectra in the case of I and II, which do not contain aromatic substituents attached to the indole ring nitrogen. For I and II in the region of aromatic protons one observes two singlets of one proton unit intensity each, which correspond to the two protons in the para position relative to one another, which is possible only for protons in the 4- and 7-positions of the indole ring for $J_{H_4H_7} < 1$ Hz. The signals of the remaining protons are in agreement with structures I and II. Thus, for II in the PMR spectrum one notes singlets for 6-CHO, 5-OCH_3, 1-NCH_3, and 2-CH_3, a triplet for CH_3, and a quartet for CH_2 of the 3-carbethoxy group; the spectrum of I is similar.

Indole derivatives with a methyl substituent in the 6-position and substituents in the 1-, 2-, 3-, and 5-positions, e.g., 1,2,6-trimethyl-3-carbethoxy-5-methoxyindole, are not formylated under the conditions of the Vilsmeier reaction; this is an indirect proof of the structures of compounds I-IV.

We have found that 2-methyl-5-methoxy-, 1,2-dimethyl-5-methoxy-, and 1-phenyl-2-methyl-5-methoxyindole* undergo Vilsmeier formylation as reported for 1-benzyl-2-methyl-5-methoxyindole [1]. Only 2-methyl-3-formyl-5-methoxyindoles V-VII are formed from 2-methyl-5-methoxyindole derivatives, which was also established by means of the PMR spectra. The PMR spectrum of VI is especially convenient for interpretation since, in the region of the aromatic protons, it contains only signals of the protons of the benzene ring. In this region one observes the presence of two doublets with spin-spin interaction constants Jmeta = 2.5 Hz and Jortho = 8.3 Hz and a quartet with the same constants. Since the possibility of migration of a OCH_3 group is excluded, this spectrum corresponds to the three protons in the 4-, 6-, and 7-positions of the benzene portion of the indole ring with an unresolved para interaction constant ($J_{H_4H_7}$), which in this case does not exceed 0.8 Hz. The signals of the protons of the remaining substituents are represented as singlets in the spectrum of VI.



I, V R=H; II VI R=CH_3; III, VII R=C_6H_5; IV R=$CH_2C_6H_5$

In an attempt to obtain 3,6-diformyl derivatives of 2-methyl-5-methoxyindoles by the action of excess Vilsmeier reagent on 2-methyl-5-methoxyindoles, the reaction, according to our observations, stops after the introduction of one formyl group into the 3-position of the indole ring.

*We obtained the starting compounds from the corresponding acids according to the method described in [2-4].

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
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TABLE 1. Formyl Derivatives of 2-Methyl-3-carbethoxy-5-methoxy- and 2-Methyl-5-methoxyindoles

Compound	mp (from alcohol)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
I	227,8—228,8	64,5	5,6	5,5	$C_{14}H_{15}NO_4$	64,4	5,8	5,4	27
III	160,5—161,5	71,3	5,6	4,4	$C_{20}H_{19}NO_4$	71,2	5,7	4,2	16
IV	156,5—157,5	72,0	6,0	4,1	$C_{21}H_{21}NO_4$	71,8	6,0	4,0	10
V	188,3—189,2	69,5	5,7	7,6	$C_{11}H_{11}NO_2$	69,8	5,9	7,4	56
VII	132,5—133,0	77,3	5,6	5,4	$C_{17}H_{15}NO_2$	77,0	5,7	5,3	81

TABLE 2. Thiosemicarbazones of Formyl Derivatives of 2-Methyl-3-carbethoxy-5-methoxy- and 2-Methyl-5-methoxyindoles

Compound	mp (decomp.)	Found, %		Empirical formula	Calc., %		Yield, %
		N	S		N	S	
VIII	234,5—235,5	16,5	9,2	$C_{15}H_{18}N_4O_3S$	16,8	9,6	97
IX	264—270	16,0	9,3	$C_{16}H_{20}N_4O_3S$	16,1	9,2	80
X	218—219	13,5	7,7	$C_{21}H_{22}N_4O_3S$	13,7	7,8	67
XI	227—228	12,9	7,4	$C_{22}H_{24}N_4O_3S$	13,2	7,5	83
XII	217,6—217,8	21,4	11,9	$C_{12}H_{14}N_4OS$	21,4	12,2	81
XIII	207,4—207,8	20,2	11,7	$C_{13}H_{16}N_4OS$	20,3	11,6	69
XIV	208,2—209,0	16,9	9,3	$C_{18}H_{18}N_4OS$	16,6	9,5	95

EXPERIMENTAL*

The PMR spectra were obtained with a JEOLCO JNM-4H-100 spectrometer with an operating frequency of 100 MHz. Carbon tetrachloride was used as the solvent for I and II, while $(CD_3)CO$ was used for VI; the internal standard was tetramethylsilane.

1,2-Dimethyl-3-carbethoxy-5-methoxy-6-formylindole (II). A total of 6.7 g (0.04 mole) of freshly distilled phosphorus oxychloride was added with stirring at 11° to a solution of 8.1 g (0.03 mole) of 1,2-dimethyl-3-carbethoxy-5-methoxyindole in 62.4 g (0.85 mole) of dimethylformamide. The solution was stirred for 1 h at room temperature, for 2.5 h at 100°, and then cooled to room temperature. It was then poured over ice, and the mixture was neutralized with stirring with a solution of 7.6 g (0.2 mole) of sodium hydroxide in 50 ml of water by adding three-fourths of the volume of the solution dropwise and one-fourth of the volume all at once; the mixture was heated rapidly with stirring to the boiling point and then allowed to cool to room temperature. The precipitate was filtered, washed with water, and dried in vacuo over calcium chloride to give 3.12 g (34%) of II with mp 135.5-136.5° (from alcohol). PMR spectrum in CCl_4 (δ, ppm): singlets at 7.44 and 7.55, $J_{H_4H_7} < 1$ Hz; singlets at 9.52 (6-CHO), 3.94 (5-OCH_3), 3.64 (1-CH_3), and 2.67 (2-CH_3); triplet at 1.45 (CH_3); quartet at 4.33 (CH_2) – (3-$COOCH_2CH_3$). Found %: C 65.5; H 6.3; N 5.2. $C_{15}H_{17}NO_4$. Calculated %: C 65.4; H 6.2; N 5.1.

Compounds I, III, and IV (see Table 1) were similarly obtained.

1,2-Dimethyl-3-formyl-5-methoxyindole (VI). A total of 5.8 g (0.038 mole) of freshly distilled phosphorus oxychloride was added dropwise with stirring to 11.7 g (0.16 mole) of dimethylformamide at 11°. The solution was stirred at the same temperature for 30 min, and 6.0 g (0.034 mole) of 1,2-dimethyl-5-methoxyindole in 8.6 g (0.12 mole) of dimethylformamide was added dropwise to it with stirring in the course of 20 min. The reaction solution was stirred at 20° for 50 min and at 35° for 45 min. It was then cooled to room temperature, poured over ice, and the resulting mixture was treated with stirring with a solution of 6.6 g (0.17 mole) of sodium hydroxide in 36 ml of water under the conditions of the previous experiment. The resulting suspension was diluted with 45 ml of water; the resulting precipitate was filtered, washed on the filter with water, and dried in vacuo over calcium chloride to give 4.8 g (69%) of VI with mp 140.7-141.7° (from alcohol). PMR spectrum in $(CD_3)_2CO$ (δ, ppm): doublet at 7.74, $J_{H_4H_7} = 2.5$ Hz; doublet at 7.32, $J_{H_6H_7} = 8.3$ Hz; quartet at 6.81, $J_{H_4H_6} = 2.5$ Hz, $J_{H_6H_7} = 8.3$ Hz, unresolved constant $J_{H_4H_7} \leq 0.8$ Hz; singlets at 11.0 (3-CHO), 3.82 (5-OCH_3), 3.69 (1-CH_3), 2.65 (2-CH_3). Found %: C 70.8; H 6.4; N 7.2. $C_{12}H_{13}NO_2$. Calculated %: C 70.9; H 6.4; N 6.8.

*R. A. Zinov'eva participated in the experimental work.

Data for compounds V and VII, obtained similarly, are presented in Table 1.

Thiosemicarbazones of I-VII (Table 2). A 23% aqueous solution of the thiosemicarbazide (1.1 moles of thiosemicarbazide was taken for 1 mole of formyl derivative) heated to 80° was added immediately to a solution of the formyl derivative in alcohol heated to the boiling point. The reaction mixture was refluxed for 30 min, cooled to room temperature, and allowed to stand overnight. The resulting precipitate was filtered, washed several times on the filter with alcohol, and dried in vacuo over calcium chloride.

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*Journal title incomplete in Russian original – Publisher.