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1957

SovietRxiv

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Abstract

Full Text

Chemistry

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SYNTHESIS OF DERIVATIVES OF 5-METHOXYINDOLE

Derivatives of 5-hydroxyindole, which underlies the structure of serotonin

$$HO-[[\text{unclear: indole structural formula}]]-CH_2CH_2NH_2,$$

a substance possessing diverse physiological properties, are of considerable interest, since many of them are very strong antimetabolites of serotonin.

In the present work we have synthesized a series of 2-aryl-5-methoxyindoles by condensation of *p*-anisidine with substituted ω-haloacetophenones.

The literature contains reports of the preparation by this route of 2-phenyl-5-methoxyindole (I) ([1]) and 2-(*p*-methoxyphenyl)-5-methoxyindole (II) ([2]); however, the experimental details, especially concerning isolation of the reaction products (which presents the greatest difficulties), were not communicated.

Fig. 1. Absorption spectrum of 2-phenyl-5-methoxyindole (I)

The structure of 2-phenyl-5-methoxyindole was proved ([1]) by the fact that on ozonization it gives N-benzoyl-5-methoxyanthranilic acid ([1]). 2-(*p*-Methoxyphenyl)-5-methoxyindole was also obtained from the extremely light- and air-sensitive *p*-methoxyphenylhydrazone of *p*-methoxyacetophenone ([3]).

The yields and properties of the compounds obtained by us are given in Table 1. The absorption spectra in the ultraviolet region for the indoles obtained are similar to one another (see Table 2 and Fig. 1).

The spectra were recorded on an SF-4 spectrophotometer. In all cases methyl alcohol was used as the solvent. In view of the poor solubility of II and VIII in methyl alcohol, for these substances the percentage absorption was determined (saturated solution, layer thickness 0.0113 cm).

3-(*p*-Methoxyphenyl)-5-methoxyindole (XII) was obtained by cyclization of (*p*-methoxyphenyl)-aminomethyl-(*p*-methoxyphenyl)-ketone (XIII) with zinc chloride.

The absorption spectra in the ultraviolet region for the starting anisidino ketone (XIII), for 2-(*p*-methoxyphenyl)-5-methoxyindole (II), and for 3-(*p*-methoxyphenyl)-5-methoxyindole (XII) differ sharply (see Fig. 2).

Table 1

No.	Starting haloacetophenone	5-Methoxyindole substituent, $R =$	Yield, %	M.p., °C	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
I	$C_6H_5COCH_2Br$	H	59	167–167.5*	170[1]					
II	4-CH_3O-$C_6H_4COCH_2Br$	2-(4-CH_3O-C_6H_4)	23	214.5–215.5*	213–214[3], 215[2]					
III	4-$CH_3C_6H_4COCH_2Cl$	2-(4-$CH_3C_6H_4$)	85	185–185.5	80.96	6.60	5.95	80.98	6.37	5.90
IV	2,5-$(CH_3O)_2C_6H_3COCH_2Cl$	2-(2,5-$(CH_3O)_2C_6H_3$)	74	174–175	71.23	6.76		81.24	6.82	
V	3,4-$(CH_3O)_2C_6H_3COCH_2Br$	2-(3,4-$(CH_3O)_2C_6H_3$)	46	147	71.12	6.91	5.63	81.24	6.82	5.75
VI	4-$BrC_6H_4COCH_2Br$	2-(4-BrC_6H_4)	36	200–205	59.54	4.10	4.68	59.61	4.00	4.64
VII	4-$ClC_6H_4COCH_2Cl$	2-(4-ClC_6H_4)	83	190.5–191	70.21	4.66	5.33	69.91	4.69	5.43
VIII	4-$C_6H_5C_6H_4COCH_2Cl$	2-(4-$C_6H_5C_6H_4$)	98	295–298	84.21	5.59	4.40	84.25	5.73	4.68
IX	4-$CH_3C_6H_4NHCOCH_2Cl$	2-(4-$CH_3C_6H_4NH$)	65	205–206	72.79	5.74		72.87	5.75	
X	4-$HOC_6H_4COCH_2Cl$	2-(4-HOC_6H_4)	40	206–207	74.82	5.76		75.29	5.47	
XI	2-$HOC_6H_4COCH_2Cl$	2-(2-HOC_6H_4)	35	162.5–163	76.35	5.46	5.90	75.92	5.47	5.85

* Above the line—our data; below the line—literature data.

Fercade and Janetzky ([4]), by the action of zinc chloride on phenacylaniline at a temperature of 180°, obtained 2-phenylindole in 39% yield. The authors proposed that the initially formed 3-phenylindole, under the action of zinc chloride at high temperature, rearranges to 2-phenylindole. The rearrangement of 3-phenylindole into 2-phenylindole on heating with zinc chloride to 180° had previously been carried out by Fischer and Schmidt ([5]). We were able to show that under milder conditions (in ethyl alcohol), on cyclization of anisidinoketone (XIII), a substituted 3-phenylindole (XIII) is indeed formed.

$$\underset{\text{XII}}{\text{CH}_3\text{O—indolinone derivative}} \xrightarrow{\text{ZnCl}_2} \underset{\text{XIII}}{\text{CH}_3\text{O—3-arylindole derivative—OCH}_3}$$

Table 2

CH_3O—indole—R

R	$\lambda_{\max}$, mμ	lg max
I —phenyl	318	4.43
II —*p*-methoxyphenyl		
III —*p*-methylphenyl	319	4.50
V —dimethylphenyl	320	4.59
VII —*p*-chlorophenyl	323	4.54
XI —*o*-hydroxyphenyl	326	4.47
IX —*p*-acetamidophenyl	326	4.54
VIII —*p*-biphenylyl	334	

The spectra were taken in the laboratory of L. A. Kazitsyna. We consider it our duty to express our gratitude to her.

Experimental Part

I. 2-Aryl-5-methoxyindoles were obtained by the following procedure: a mixture of 5 moles of *p*-anisidine and 1 mole of ω-haloacetophenone was heated for 15 min at 180–200°. The cooled reaction mixture was dissolved in a minimum amount of methyl alcohol and poured into approximately a tenfold volume of hydrochloric acid (1:4). The resulting precipitate was dried in a vacuum desiccator over calcium chloride.

2-Phenyl-5-methoxyindole (I) was crystallized from methyl alcohol.

2-(*p*-Methoxyphenyl)-5-methoxyindole (II), and also **2-(*p*-bromophenyl)-5-methoxyindole (VI)**, were purified by crystallization from carbon tetrachloride and then from methyl alcohol.

2-(*p*-Chlorophenyl)-5-methoxyindole (VII) was crystallized from carbon tetrachloride and then from ethyl alcohol.

2-(*p*-Tolyl)-5-methoxyindole (III) was crystallized from a mixture of benzene and isooctane, and then from benzene.

2-(*p*-Xylyl)-5-methoxyindole (IV) was extracted with isooctane and, after removal of the solvent, crystallized from methyl alcohol.

Fig. 2. Absorption spectra of 2-(*p*-methoxyphenyl)-5-methoxyindole (II), 3-(*p*-methoxyphenyl)-5-methoxyindole (XII), and (*p*-methoxyphenyl)-aminomethyl-(*p*-methoxyphenyl)-ketone (XIII). Saturated solutions. $d = 0.0113$ cm

Figure 2: Fig. 2. Absorption spectra of 2-(*p*-methoxyphenyl)-5-methoxyindole (II), 3-(*p*-methoxyphenyl)-5-methoxyindole (XII), and (*p*-methoxyphenyl)-aminomethyl-(*p*-methoxyphenyl)-ketone (XIII). Saturated solutions. $d = 0.0113$ cm

2-(*o*-Xylyl)-5-methoxyindole (V) was extracted with ether; the ethereal solution was purified by boiling with Al_2O_3; after removal of the ether, it was treated with a benzene–isooctane mixture. The resulting substance was crystallized from benzene and then from aqueous methyl alcohol.

2-(*p*-Biphenyl)-5-methoxyindole (VIII) was crystallized from toluene.

2-(*p*-Acetaminophenyl)-5-methoxyindole (IX) was crystallized from acetic acid and then from methyl alcohol.

2-(*p*-oxyphenyl)-5-methoxyindole (X) was extracted with isooctane and, after removal of the solvent, crystallized from benzene.

2-(*o*-oxyphenyl)-5-methoxyindole (XI) was extracted with benzene; the solution was boiled with Al_2O_3, and, after evaporation of the solvent, crystallized from a benzene–isooctane mixture.

II. Preparation of (*p*-methoxyphenyl)-aminomethyl-(*p*-methoxyphenyl)-ketone (XIII). 9.84 g of *p*-anisidine was added to a solution of 9.16 g of *p*-methoxy-ω-bromoacetophenone in 30 ml of ethyl alcohol. After half an hour the precipitated anisidinoketone was filtered off. By evaporating the mother liquor, an additional amount of anisidinoketone was obtained. The total yield was 9.5 g (88%). Mp 126–127° (from alcohol).

$C_{16}H_{17}O_3N$.	Found, %:	N 5.11
	Calculated, %:	N 5.16

III. Preparation of 3-(*p*-methoxyphenyl)-5-methoxyindole (XII). 5 g of (*p*-methoxyphenyl)-aminomethyl-(*p*-methoxyphenyl)-ketone and 10 g of zinc chloride were dissolved in 20 ml of absolute ethyl alcohol and heated for 7 h to boiling. The reaction mixture was poured into 150 ml of hydrochloric acid (1:4). The resulting precipitate was dried in a vacuum desiccator over calcium chloride; the indole was extracted from it with isooctane. 1.1 g (23%) of 3-(*p*-methoxyphenyl)-5-methoxyindole was obtained; it was recrystallized from methyl alcohol. Mp 151.5–152°.

Fig. 2. Absorption spectra of 2-(*p*-methoxyphenyl)-5-methoxyindole (II), 3-(*p*-methoxyphenyl)-5-methoxyindole (XII), and (*p*-methoxyphenyl)-aminomethyl-

(*p*-methoxyphenyl)-ketone (XIII). Saturated solutions. $d = 0.0113$ cm.

$C_{16}H_{15}O_2N$.	Found, %:	C 75.94; 75.52; H 6.39; 6.16; N 5.75
	Calculated, %:	C 75.86; H 5.97; N 5.53

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Received
28 I 1957

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Note: Figure translations are in progress. See original paper for figures.