SYNTHESIS OF ALDEHYDES AND NITRILES IN THE 5-HYDROXYINDOLE SERIES

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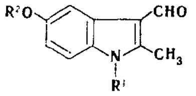
A preparative method for the synthesis of previously inaccessible 3-formyl-5-hydroxyindole derivatives by Vilsmeier formylation of 5-acetoxyindoles is proposed. 5-Hydroxyindole-3-carboxylic acid nitriles and their 4-dimethylamino-methyl derivatives were obtained from 3-formyl-5-hydroxyindoles through their oximes.

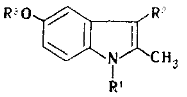
We have found that 2-methyl-5-acetoxyindoles, like 2-methyl-5-methoxyindoles [1], undergo Vilsmeier formylation in the 3 position. The formyl group is not involved in the alkaline hydrolysis of the resulting 2-methyl-3-formyl-5-acetoxyindoles (Ia-c), but the acetyl protective group is easily removed to give 2-methyl-3-formyl-5-hydroxindoles (IIa-c). Thus we have found a method for the synthesis of the previously inaccessible 3-formyl-5-hydroxyindole derivatives [2].

A quartet with J = 9.0 and 2.5 Hz, a doublet with J = 9.0 Hz, and a doublet with J = 2.5 Hz, which are related, respectively, to the 6-H, 7-H, and 4-H protons, are observed in the PMR spectra of IIa-c. The spectra are distinguished by the singlet of the proton of the formyl group at 10 ppm. All of this proves that the formyl group enters precisely the 3 position. The presence of CH_3CO, HO, and CHO functional groups in Ia-c and IIa-c is confirmed by the IR spectra (see Table 1). We obtained the oximes (IIIa-c) of 2-methyl-3-formyl-5-hydroxyindoles by the usual method. When oximes IIIa-c are heated with acetic anhydride they undergo dehydration, and the hydroxyl group in the 5 position is simultaneously acetylated. We used this method to obtain 2-methyl-5-acetoxyindole-3-carboxylic acid nitriles (IVa-c) and obtained 2-methyl-5-hydroxy-3-carboxylic acid nitriles (Va-c) by selective hydrolysis of the 5-acetoxy group of IVa-c.

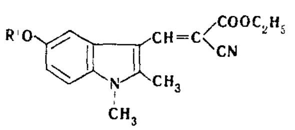
We obtained the esters of the corresponding acrylic acids (VI, VII) by condensation of 1,2-dimethyl-3-formyl-5-acetoxy- and 1,2-dimethyl-3-formyl-5-hydroxyindole with cyanoacetic ester in pyridine in the presence of small amounts of piperidine.



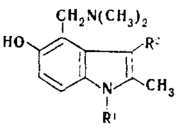
I–II



III–V



VI–VII



VIII–IX

I—II, a $R^1=CH_3$, b $R^1=C_6H_5$, c $R^1=CH_2C_6H_5$; Ia–c $R^2=CH_3CO—$; IIa–c $R^2=H$; III—V, a $R^1=CH_3$, b $R^1=C_6H_5$, c $R^1=CH_2C_6H_5$; IIIa—c $R^2=CH{=}NOH$, $R^3=H$; IVa–c $R^2=C\equiv N$, $R^3=CH_3CO$; Va—c $R^2=C\equiv N$, $R^3=H$;
VI $R^1=CH_3CO$; VII $R^1=H$; VIII—IX, a $R^1=CH_3$, b $R^1=C_6H_5$, c $R^1=CH_2C_6H_5$; VIIIa–c $R^2=CHO$; IXa—c $R^2=C\equiv N$; X $R^1=CH_3$, $R^2=CH{=}C(COOC_2H_5)CN$

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Empirical formula	Found, %			Calc., %			IR spectrum, cm^{-1}	Yield, %
			C	H	N	C	H	N		
Ia	189,5—190,5	$C_{13}H_{13}NO_3$	67,4	5,7	6,2	67,5	5,7	6,1	1645 (CHO—); 1740 (CH_3CO—)	68
Ib	205,7—206,7	$C_{18}H_{15}NO_3$	74,0	5,1	—	73,7	5,2	—	1657 (CHO—); 1754 (CH_3CO—)	50
Ic	212,7—213,7	$C_{19}H_{17}NO_3$	74,6	6,0	—	74,3	5,6	—	1657 (CHO—); 1754 (CH_3CO—)	47
IIa	264,5—265,5	$C_{11}H_{11}NO_2$	70,1	5,5	7,2	69,8	5,8	7,4	1610 (CHO—); 3190 (—OH)	60
IIb	261,3—262,3	$C_{16}H_{13}NO_2$	76,3	5,1	5,6	76,5	5,2	5,6	1620 (CHO—); 3220 (—OH)	53
IIc	251,9—252,9	$C_{17}H_{15}NO_2$	77,2	5,5	5,4	77,0	5,7	5,3	1630 (CHO—); 3190 (—OH)	70
IIIa	204,6—205,6	$C_{11}H_{12}N_2O_2$	64,5	5,9	13,8	64,7	5,9	13,7	1635 (—CH=NOH); 3345 (—OH)	70
IIIb	181,4—182,0	$C_{16}H_{14}N_2O_2$	71,9	5,4	10,4	72,2	5,3	10,5	1627 (—CH=NOH); 3385 (—OH)	65
IIIc	193,2—194,2	$C_{17}H_{16}N_2O_2$	72,8	5,7	10,0	72,8	5,8	10,0	1623 (—CH=NOH); 3475 (—OH)	74
IVa	154,3—155,0	$C_{13}H_{12}N_2O_2$	68,2	5,2	12,4	68,4	5,3	12,3	1750 (CH_3CO—); 2200 (—CN)	86
IVb	128,6—129,2	$C_{18}H_{14}N_2O_2$	74,4	4,9	9,8	74,5	4,9	9,7	1760 (CH_3CO—); 2210 (—CN)	60
IVc	191,4—192,0	$C_{19}H_{16}N_2O_2$	—	—	9,0	—	—	9,2	1755 (CH_3CO—); 2230 (—CN)	56
Va	203,0—204,0	$C_{11}H_{10}N_2O$	70,8	5,4	14,8	71,0	5,4	15,0	2220 (—CN); 3335 (—OH)	80
Vb	229,3—229,8	$C_{16}H_{12}N_2O$	—	—	11,2	—	—	11,3	2230 (—CN); 3335 (—OH)	68
Vc	186,1—186,6	$C_{17}H_{14}N_2O$	77,8	5,7	10,7	77,8	5,4	10,7	2230 (—CN); 3328 (—OH)	67
VI	156,9—157,4	$C_{18}H_{18}N_2O_4$	66,3	5,6	8,5	66,3	5,6	8,6	1755 (CH_3CO—); 1715 (C_2H_5OCO—); 2220 (—CN)	61
VII	188,6—189,2	$C_{16}H_{16}N_2O_3$	67,6	5,7	9,7	67,6	5,7	9,9	1670 (C_2H_5OCO—); 2228 (—CN); 3335 (—OH)	57
VIIIa	158,3—158,8	$C_{14}H_{18}N_2O_2$	68,2	7,4	11,2	68,3	7,4	11,4	1620 (CHO—)	75
VIIIb	150,6—151,6	$C_{19}H_{20}N_2O_2$	74,1	6,6	8,6	74,0	6,5	9,1	1620 (CHO—)	68
VIIIc	121,1—121,9	$C_{20}H_{22}N_2O_2$	74,0	6,9	8,4	74,5	6,9	8,7	1645 (CHO—)	62
IXa	186,8—187,3	$C_{14}H_{17}N_3O$	69,0	7,0	17,4	69,1	7,0	17,3	2200 (—CN)	66
IXb	152,3—153,0	$C_{19}H_{19}N_3O$	75,0	6,4	13,6	74,7	6,3	13,8	2200 (—CN)	77
IXc	143,0—143,5	$C_{20}H_{21}N_3O$	—	—	12,9	—	—	13,2	2220 (—CN)	65
X	176,8—177,8	$C_{19}H_{23}N_3O_3$	56,9	6,7	12,3	66,8	6,8	12,3	1715 (C_2H_5OCO—); 2220 (—CN)	95

The corresponding 4-dimethylaminomethyl derivatives (VIIIa-c, IXa-c, and X) are formed in the reaction of IIa-c, Va-c, and VII with bis(dimethylamino)methane in a mixture of dioxane and dimethylformamide (DMF). The absorption band of the hydroxyl group in the spectra of both concentrated and dilute solutions vanishes when there is a dimethylaminodimethyl group in the ortho position relative to the hydroxyl group, and this is explained by the formation of an intramolecular hydrogen bond [3]. Pronounced absorption of the OH group at 3335 cm^{-1} is observed in the spectra of the hydrochlorides of these same substances.

EXPERIMENTAL*

The PMR spectra of deuterodimethyl sulfoxide solutions of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra were recorded with Perkin-Elmer and UR-10 spectrometers. The physical constants, yields, and IR spectra data for the synthesized compounds are presented in Table 1.

1,2-Dimethyl-3-formyl-5-acetoxyindole (Ia). A 1.0-ml [1.7 g (10.3 mmole)] sample of freshly distilled phosphorus oxychloride was added dropwise at 10° to 3.6 ml [3.46 g (46.3 mmole)] of dry DMF, after which the mixture was stirred at 20° for 3 min. A solution of 2 g (9.8 mmole) of 1,2-dimethyl-5-acetoxyindole [4] in 3.7 ml [3.5 mmole)] of dry DMF was then added dropwise with stirring at 20° to the resulting brownish-red solution, after which the mixture was stirred at 20° for 30 min and at 45° for 45 min. It was then cooled and poured into a mixture of ice and water (~15 g). A solution of 1.3 g (32.7 mmole) of sodium hydroxide in 21 ml of water was then added dropwise with stirring to the resulting solution, the mixture was diluted with 20 ml of water, and the precipitated Ia was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol.

Compounds Ib and Ic were similarly obtained (see Table 1).

1,2-Dimethyl-3-formyl-5-hydroxyindole (IIa). A) 1,2-Dimethyl-5-acetoxyindole was formylated as in the synthesis of Ia. The reaction mixture was poured over ice, after which a solution of 3.8 g (94.5 mmole) of sodium hydroxide in 21 ml of water was added dropwise with stirring to the aqueous mixture. It was then diluted with 21 ml of water, and the solid material was allowed to dissolve for 15 min. The solution was then filtered, and acetic acid was added to the filtrate to pH 6. The precipitated IIa was removed by filtration, washed on the filter with water, and dried. PMR spectrum, δ, ppm: 6.69 q† (6-H), 7.31 d (7-H), 7.53 d (4-H), 9.14 s (5-OH), and 10.00 s (3-CHO).

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

†Here and subsequently, q is quartet, d is doublet, and s is singlet.

B) A 0.5-g (2.2 mmole) sample of Ia was refluxed at 70° for 30 min with 29 ml of a 10% solution of potassium hydroxide in methanol, and the resulting solution was filtered. The filtrate was diluted with 360 ml of water and acidified with acetic acid to pH 6. The precipitated IIa was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol.

Compounds IIb and IIc were similarly obtained. PMR spectrum of IIb, δ, ppm: 6.55 q (6-H), 6.83 d (7-H), 7.60 d (4-H), 9.05 s (5-OH), and 10.10 s (3-CHO). PMR spectrum of IIc, δ ppm: 6.63 q (6-H), 7.18 d (7-H), 7.52 d (4-H), 9.00 s (5-OH), and 10.02 s (3-CHO).

1,2-Dimethyl-3-formyl-5-hydroxyindole Oxime (IIIa). A mixture of 1 g (5.3 mmole) of IIa, 14.8 ml of absolute alcohol, 2.2 g (31.9 mmole) of hydroxylamine hydrochloride, and 7.4 ml of dry pyridine was refluxed at 100° for 2 h, after which it was vacuum evaporated at 40° (12 mm), and 30 ml of water was added to the residue. The precipitated IIIa was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol.

Compounds IIIb and IIIc were similarly synthesized.

1,2-Dimethyl-5-acetoxyindole-3-carboxylic Acid Nitrile (IVa). A mixture of 1.5 g (7.4 mmole) of IIIa and 20 ml [21.6 g (211.6 mmole)] of acetic anhydride was refluxed at 140° for 4 h, after which it was cooled and poured into a fivefold volume of water. The precipitated IVa was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol or aqueous alcohol.

Compounds IVb and IVc were similarly synthesized.

1,2-Dimethyl-5-hydroxyindole-3-carboxylic Acid Nitrile (Va). A 2.7-g (11.8 mmole) sample of IVa was refluxed at 70° with 154.8 ml of a 10% solution of potassium hydroxide in methanol for 30 min, after which the mixture was cooled to room temperature and poured into 720 ml of water. The aqueous solution was filtered, and the filtrate was acidified with acetic acid. The precipitated Va was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol or aqueous alcohol.

Compounds Vb and Vc were similarly synthesized.

Ethyl 3^1-(1,2-dimethyl-5-acetoxy-3-indolyl)-2^1-cyanoacrylate (VI). A mixture of 2.9 g (12.6 mmole) of Ia, 2 g (19.2 mmole) of cyanoacetic ester, 48 ml of dry pyridine, and 0.4 ml (eight drops) of pyridine was allowed to stand for 24 h at 20°, after which it was poured into 200 ml of water. The resulting precipitate was removed by filtration, washed on the filter with water, and dried. The dry reaction product (3.4 g) was heated with 34 ml of acetic anhydride at 100° for 2 h, after which the mixture was cooled to room temperature and poured into 340 ml of water. The precipitated VI was removed by filtration, washed on the filter with water, and dried to give 3.1 g of product, which was recrystallized from alcohol. See Table 1 for data on ester VI.

Ethyl 3^1-(1,2-Dimethyl-5-hydroxy-3-indolyl)-2^1-cyanoacrylate (VII). A mixture of 1.8 g (9.5 mmole) of IIa, 1.5 g (14.4 mmole) of cyanoacetic ester, 36 ml of dry pyridine, and 0.3 ml (six drops) of pyridine was allowed to stand at 20° for 3 days. The resulting solution was poured into 250 ml of water, and the precipitated VII was removed by filtration, washed on the filter with water, dried, and recrystallized from alcohol.

1,2-Dimethyl-3-formyl-4-dimethylaminomethyl-5-hydroxyindole (VIIIa). A mixture of 1 g (5.5 mmole) of IIa, 0.8 g (7.9 mmole) of bis(dimethylamino)methane, 6.9 ml of dioxane, and 2.7 ml of DMF was refluxed at 100° for 2.5 h (the reflux condensor was fitted with a soda-lime tube). The mixture was vacuum evaporporated (at 12 mm and 50°), 133 ml of waters was added to the residue, and the aqueous mixture was extracted with ether. The ether was removed from the extract by distillation, water was added to the residue, and the precipitated VIIIa was removed by filtration, washed onthe filter with water, dried over solid alkali in a vacuum desiccator, and recrystallized from alcohol.

Compounds VIIIb and VIIIc were similarly synthesized.

3-Cyano-1,2-dimethyl-4-dimethylaminomethyl-5-hydroxyindole (IXa). A mixture of 1 g (5.4 mmole) of Va, 1.6 g (15.5 mmole) of bisdimethylaminomethane, and 18.3 g of dry dioxane was heated at 100° for 4 h in a flask equipped with a reflux condenser with a soda-lime tube. It was then cooled to room temperature and poured into 150 ml of water. The precipitated IXa was removed by filtration, washed on the filter with water, dried over calcium chloride and solid alkali in a vacuum desiccator, and recrystallized from alcohol.

Hydrochloride of IXa. Base IXa was dissolved in the minimum volume of acetone, and an ether solution of hydrogen chloride was added to the acetone solution until precipitation was complete (excess hydrogen chloride was avoided). The precipitated hydrochloride of IXa was isolated and recrystallized from absolute alcohol.

Compounds IXb and IXc and their hydrochlorides were similarly synthesized.

Ethyl 3'-(1,2-Dimethyl-4-dimethylaminomethyl-5-hydroxy-3-indolyl)-2'-cyanoacrylate (X). A mixture of 0.5 g (1.8 mmole) of VI, 0.5 g (5.1 mmole) of bis(dimethylamino)methane, and 6 ml of dry dioxane was refluxed at 100° for 4 h (the condenser was fitted with a soda-lime tube). It was then cooled to room temperature and poured into 50 ml of water. The precipitated X was removed by filtration, washed on the filter with water, and dried over solid alkali in a vacuum desiccator. A sample of the dry product (0.6 g) was recrystallized from alcohol.

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