Synthesis of 5-hydroxy-*N*-(2-vinyloxyalkyl)indoles from dicarbonyl compounds and vinyloxyalkylamines

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N-(Vinyloxyalkyl)enaminoketones were obtained by the condensation of vinyloxyalkylamines with acetylacetone or ethyl acetoacetate. Their subsequent reactions with 1,4-benzoquinone produce the corresponding 5-hydroxy-2-methyl-*N*-(2-vinyloxyalkyl)indoles in 17—43% yields. The structures of the compounds obtained were confirmed by IR and ^{1}H NMR spectroscopy.

Key words: 3-acetyl-5-hydroxy-2-methyl-*N*-(2-vinyloxyalkyl)indoles, ethyl 5-hydroxy-2-methyl-*N*-(2-vinyloxyalkyl)indole-3-carboxylates, vinyloxyalkylamines, enaminoketones.

5-Hydroxyindole derivatives possess hypotensive, antihistaminic, and psychotropic activity.[1,2]

We pioneered the synthesis of 5-hydroxyindoles containing vinyloxyalkyl substituents at the N atom, which are therefore of interest as synthons (carriers of the indole ring) in reactions of the vinyl group, including their role as monomers for preparing indole-containing polymers.

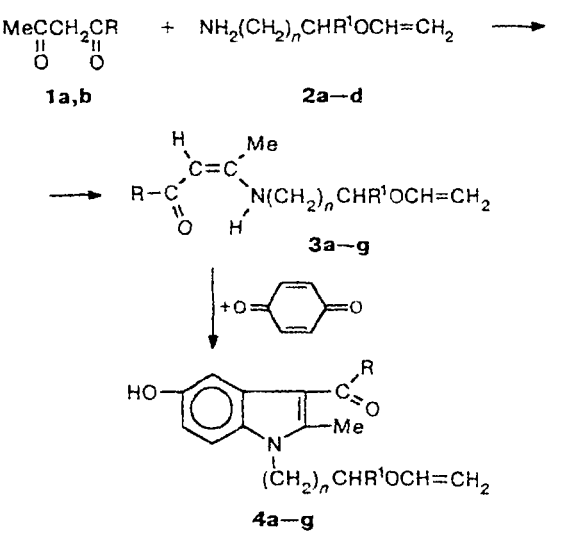
The condensation of acetylacetone (**1a**) with vinyloxyalkylamines (**2a—d**) occurs when the reagents are simply mixed and results in the formation of enaminoketones (**3a—d**) in 82—95% yields (Scheme 1). In the case of vinyloxy-1,1-dimethylethylamine (**5**) with the sterically hindered amino group and in the condensation of vinyloxyalkylamines (**2a—c**) with ethyl acetoacetate **1b**, enamines (**3e—g**, **6**) could be obtained when the reactions were performed in boiling benzene with azeotropic distillation of water (yields 71—78%).

The reactions of enamines **3e—g** with 1,4-benzoquinone were carried out as in the known method[3] by boiling a mixture of the reagents in an acetone solution (Nenitzescu synthesis). Indoles **4a—g** were obtained in low yields (17—43%) (see Scheme 1).

In the ^{1}H NMR spectra of indoles **4a—g**, the signals of protons of the vinyloxy group are presented by doublets of doublets with δ from 3.85 to 4.02 (for *cis*-OC=CH), from 4.09 to 4.20 (for *trans*-OC=CH), and from 6.08 to 6.53 (for OCH=C) with spin-spin coupling constants $^2J_{gem}$ = 2.0—2.2, $^3J_{cis}$ = 6.5—6.8, and $^3J_{trans}$ = 13.8—14.2 Hz, respectively. The signals of protons of the aromatic ring appear as a doublet of doublets with δ 6.69—6.71 (for C(6)—H) and usually strongly overlapping doublets for C(7)—H (δ ~7.30) and C(4)—H (δ ~7.38) with spin-spin coupling constants ^3J = 8.6—8.8 and ^4J = 2.0—2.2 Hz. In the spectra of some indoles, signals of protons of the NCH_2 and OCH_2 groups completely or partially overlap with the signals of geminal protons of the vinyloxy group, and signals of protons of C(6)—H overlap with the signals of protons of OCH=C to form complex multiplets. For a more exact assignment of signals in these multiplets, we synthesized indole **7** devoid of vinyloxy group (Scheme 2).

An attempt to prepare the indole from enaminoketone **6** containing the sterically hindered amino group re-

Scheme 1



1a: R = Me; **1b:** R = OEt; **2a:** R^1 = H, *n* = 1; **2b:** R^1 = Me, *n* = 1; **2c:** R^1 = H, *n* = 2; **2d:** R^1 = H, *n* = 3; **3a, 4a:** R = Me, R^1 = H, *n* =1; **3b, 4b:** R = R^1 = Me, *n* = 1; **3c, 4c:** R = Me; R^1 = H, *n* = 2; **3d, 4d:** R = Me, R^1 = H, *n* = 3; **3e, 4e:** R = OEt; R^1 = H, *n* = 1; **3f, 4f:** R = OEt, R^1 = Me, *n* = 1; **3g, 4g:** R = OEt, R^1 = H, *n* = 2

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 12, pp. 2228—2231, December, 1997.

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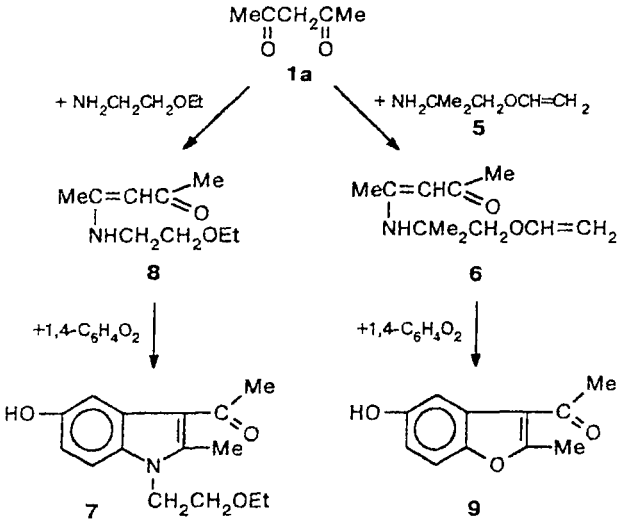
Scheme 2



sulted in the isolation of only product **9**. This compound contains no N atoms and, based on the elemental analysis and ^{1}H NMR spectroscopic data, it is a derivative of benzo[*b*]furan (see Scheme 2).

Experimental

^{1}H NMR spectra were recorded on a JEOL FX 90Q instrument (90 MHz, HMDS as the internal standard) at 30 °C. IR spectra were recorded on a Specord 75-IR spectrophotometer in a thin layer (for liquids) and in KBr (for solids).

The purity of compounds was monitored by GLC on an LKhM-80 chromatograph using katharometer as the detector, helium as the carrier gas, and a steel column (3000×3 mm) with 3% OV-17 on Inerton Super (0.160—0.200 mm) in the temperature-programmed regime (90—300 °C) at a rate of 4 deg min^{-1}.

Synthesis of enamines 3a—d. Vinyloxyalkylamine **2a—d** (0.1 mol) was added to acetylacetone **1a** (0.1 mol) with stirring at a temperature not higher than 45 °C. Enamines **3a—d** were isolated by distillation *in vacuo*.

Table 1. Yields and characteristics of synthesized compounds **3a—g, 4a—g, 6—9**

Compound	Yield (%)	B.p./°C (*p*/Torr)	M.p./°C	n_D^{20}	d_4^{20}	Found / Calculated (%) C	H	N	Molecular formula
3a	95	132—133 (6)	35—38[a]			64.08 63.88	8.48 8.93	8.27 8.28	$C_9H_{15}NO_2$
3b	91	150—153 (7)		1.5162	0.9890	66.29 65.54	9.74 9.35	7.28 7.64	$C_{10}H_{17}NO_2$
3c	82	138—140 (3)		1.5250	1.0004	66.05 65.54	9.50 9.35	7.14 7.64	$C_{10}H_{17}NO_2$
3d	82	144—146 (3)		1.5205	0.9876	66.25 66.97	9.53 9.71	7.02 7.10	$C_{11}H_{19}NO_2$
3e	78	129—131 (5)		1.5145	1.0371	60.51 60.28	8.41 8.60	7.00 7.03	$C_{10}H_{17}NO_3$
3f	74	165—168 (15)		1.5002	1.0200	61.88 61.95	9.02 8.98	6.61 6.57	$C_{11}H_{19}NO_3$
3g	71	150—153 (4)		1.5025	1.0208	62.07 61.95	9.01 8.98	6.89 6.57	$C_{11}H_{19}NO_3$
4a	28		176			69.52 69.47	6.48 6.61	5.25 5.40	$C_{15}H_{17}NO_3$
4b	43		162			70.52 70.29	7.08 7.01	4.97 5.13	$C_{16}H_{19}NO_3$
4c	32		166			70.30 70.29	7.27 7.01	5.03 5.13	$C_{16}H_{19}NO_3$
4d	21		157			71.70 71.04	7.25 7.37	4.93 4.88	$C_{17}H_{21}NO_3$
4e	24		144			66.77 66.41	6.48 6.62	5.03 4.84	$C_{16}H_{19}NO_4$
4f	17		142			67.56 67.29	7.14 6.98	4.45 4.62	$C_{17}H_{21}NO_4$
4g	21		135			67.12 67.29	7.06 6.98	4.52 4.62	$C_{17}H_{21}NO_4$
6	73	116—120 (4)		1.5220	1.0042	66.29 66.97	9.54 9.71	7.12 7.10	$C_{11}H_{19}NO_2$
7	54		205			69.11 68.94	7.18 7.33	5.21 5.36	$C_{15}H_{19}NO_3$
8	81	135—138 (4)		1.5090	0.9843	63.26 63.13	10.07 10.01	8.21 8.18	$C_9H_{17}NO_2$
9	12		225			69.17 69.46	5.14 5.30		$C_{11}H_{10}O_3$

[a] Ref. 4: m.p. 34—35 °C.

Table 2. Data of IR and ^{1}H NMR spectra for compounds **3a—g, 4a—g, 6—9**

Compound	IR, ν/cm^{-1}	^{1}H NMR ($CDCl_3$), δ (J/Hz)
3a	1510, 1560, 1620 (C=C—C=O, C=C); 3075, 3115 (=CH); 3350 (NH)	1.93 (s, 3 H, C=C—Me); 1.97 (s, 3 H, O=C—Me); 3.52 (dt, 2 H, NCH_2); 3.77 (t, 2 H, OCH_2); 4.01 (dd, 1 H, *cis*-C=CH); 4.16 (dd, 1 H, *trans*-C=CH); 4.98 (s, 1 H, C=CH—C=O); 6.46 (dd, 1 H, OCH=C); 10.93 (br.s, 1 H, NH)
3b	1500, 1570, 1600, 1630 (C=C—C=O, C=C); 3070, 3110 (=CH); 3400 (NH)	1.24 (d, 3 H, Me); 1.91 (s, 3 H, C=C—Me); 1.97 (s, 3 H, O=C—Me); 3.31 (dd, 2 H, NCH_2); 3.95 (m, 1 H, OCH); 4.01 (dd, 1 H, *cis*-C=CH); 4.27 (dd, 1 H, *trans*-C=CH); 4.95 (s, 1 H, C=CH—C=O); 6.29 (dd, 1 H, OCH=C); 10.80 (br.s, 1 H, NH)
3c	1500, 1520, 1570, 1595, 1620 (C=C—C=O, C=C); 3070, 3110 (=CH); 3350 (NH)	1.82 (m, 2 H, CCH_2C); 1.90 (s, 3 H, C=CMe); 1.95 (s, 3 H, Me); 3.34 (dt, 2 H, NCH_2); 3.71 (t, 2 H, OCH_2); 3.97 (dd, 1 H, *cis*-C=CH); 4.17 (dd, 1 H, *trans*-C=CH); 4.93 (s, 1 H, C=CH—C=O); 6.43 (dd, 1 H, OCH=C); 10.84 (br.s, 1 H, NH)
3d	1500, 1560, 1600, 1620 (C=C—C=O, C=C); 3030, 3060, 3120 (=CH); 3300 (NH)	1.71 (m, 4 H, CCH_2CH_2C); 1.91 (s, 3 H, C=C—Me); 1.97 (s, 3 H, O=C—Me); 3.27 (dt, 2 H, NCH_2); 3.69 (t, 2 H, OCH_2); 3.97 (dd, 1 H, *cis*-C=CH); 4.15 (dd, 1 H, *trans*-C=CH); 4.95 (s, 1 H, C=CH—C=O); 6.45 (dd, 1 H, OCH=C); 10.86 (br.s, 1 H, NH)
3e	1500, 1600, 1650 (C=C—C=O, C=C); 3055, 3100 (=CH); 3275 (NH)	1.23 (t, 3 H, OCMe); 1.92 (s, 3 H, C=C—Me); 3.50 (dt, 2 H, NCH_2), 3.77 (t, 2 H, OCH_2); 4.01—4.21 (m, 4 H, *cis*-C=CH, $COOCH_2$, *trans*-C=CH); 4.46 (s, 1 H, C=CH—C=O); 6.47 (dd, 1 H, OC=CH); 8.70 (br.s, 1 H, NH)
3f	1500, 1600, 1660 (C=C—C=O, C=C); 3060, 3100, 3170 (=CH); 3280 (NH)	1.27 (m, 6 H, OCMe, CHMe); 2.15 (s, 3 H, C=C—Me); 3.43 (m, 2 H, NCH_2); 3.78—4.21 (m, 5 H, OCH, *cis*-C=CH, $COOCH_2$, *trans*-C=CH); 4.46 (s, 1 H, C=CH—C=O); 6.47 (dd, 1 H, OCH=C); 8.84 (br.s, 1 H, NH)
3g	1500, 1600, 1650 (C=C—C=O, C=C); 3030, 3070, 3100, 3170 (=CH); 3285 (NH)	1.22 (t, 3 H, OCMe); 1.89 (m, 5 H, CCH_2C, C=C—Me); 3.34 (dt, 2 H, NCH_2); 3.73 (t, 2 H, OCH_2); 4.00—4.20 (m, 4 H, *cis*-C=CH, $COOCH_2$, *trans*-C=CH); 4.43 (s, 1 H, C=CH—C=O); 6.44 (dd, 1 H, OCH=C); 8.59 (br.s, 1 H, NH)
4a	1500, 1590, 1620, 3070, 3200	[a]2.51 (s, 3 H, C=C—Me); 2.68 (s, 3 H, O=C—Me); 3.94 (m, 3 H, NCH_2, *cis*-C=CH); 4.16 (dd, 1 H, *trans*-C=CH, $^2J_{gem}$ = 2.0, $^3J_{trans}$ = 14.2); 4.44 (t, 2 H, OCH_2); 6.40 (dd, 1 H, OCH=C, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.2); 6.68 (dd, 1 H, C(6)H, ^3J = 8.7, ^4J = 2.2); 7.34—7.39 (m, 2 H, C(4)H, C(7)H); 9.05 (s, 1 H, OH)
4b	1500, 1585, 1600, 1620, 3065, 3190	[a]1.25 (d, 3 H, Me); 2.51 (s, 3 H, C=C—Me); 2.70 (s, 3 H, O=C—Me); 3.81 (dd, 1 H, *cis*-C=CH); 4.00 (m, 4 H, NCH_2, *trans*-C=CH, OCH); 6.12 (dd, 1 H, OCH=C); 6.69 dd, 1 H, C(6)H); 7.31—7.41 (m, 2 H, C(4)H, C(7)H); 8.97 (s, 1 H, OH)
4c	1500, 1580, 1600, 1605, 3070, 3190	[a]1.98 (m, 2 H, CCH_2C); 2.49 (s, 3 H, C=C—Me); 2.65 (s, 3 H, O=C—Me); 3.94—4.23 (m, 6 H, NCH_2, *cis*-C=CH, *trans*-C=CH, OCH_2); 6.53 (dd, 1 H, OCH=C); 6.69 (dd, 1 H, C(6)H); 7.35—7.40 (m, 2 H, C(4)H, C(7)H); 9.12 (s, 1 H, OH)
4d	1495, 1580, 1610, 3070, 3190	[a]1.69 (m, 4 H, CCH_2CH_2C); 2.48 (s, 3 H, C=C—Me); 2.66 (s, 3 H, O=C—Me); 3.66 (t, 2 H, NCH_2); 3.91 (dd, 1 H, *cis*-C=CH); 3.85—4.23 (m, 3 H, *trans*-C=CH, OCH_2); 6.45 (dd, 1 H, OCH=C); 6.66 (dd, 1 H, C(6)H); 7.25—7.42 (m, 2 H, C(4)H, C(7)H); 8.95 (s, 1 H, OH)
4e	1510, 1610, 1645, 3050, 3300	[a]1.40 (t, 3 H, CH_2Me); 2.51 (q, 2 H, CH_2Me); 2.69 (s, 3 H, O=C—Me); 3.86—4.48 (m, 6 H, NCH_2, *cis*-C=CH, *trans*-C=CH, OCH_2); 6.45 (dd, 1 H, OCH=C); 6.71 (dd, 1 H, C(6)H); 7.36—7.45 (m, 2 H, C(4)H, C(7)H); 9.05 (s, 1 H, OH)
4f	1510, 1615, 1660, 3040, 3220	[a]1.31 (m, 6 H, CHMe, CH_2Me); 2.49 (q, 2 H, CH_2Me); 2.68 (s, 3 H, O=C—Me); 3.78 (dd, 1 H, *cis*-C=CH); 3.86—4.28 (m, 4 H, NCH_2, *trans*-C=CH, OCH); 6.08 (dd, 1 H, OCH=C); 6.67 (dd, 1 H, C(6)H); 7.28—7.40 (m, 2 H, C(4)H, C(7)H); 8.90 (s, 1 H, OH)
4g	1510, 1610, 1650, 3050, 3250	[a]1.34 (m, 3 H, CH_2Me); 1.98 (m, 2 H, CCH_2C); 2.49 (q, 2 H, CH_2Me); 2.65 (s, 3 H, O=C—Me); 3.62 (t, 2 H, NCH_2); 3.86—4.28 (m, 4 H, *cis*-C=CH, *trans*-C=CH, OCH_2); 6.43—6.75 (m, 2 H, OCH=C, C(6)H); 7.26 (d, 1 H, C(7)H, ^3J = 8.8); 7.38 (d, 1 H, C(4)H, ^4J = 2.1); 8.91 (s, 1 H, OH)
6	1500, 1600, 1650 (C=C—C=O, C=C); 3060, 3100 (=CH); 3295 (NH)	1.40 (m, 6 H, CMe_2); 1.96 (s, 3 H, C=C—Me); 2.04 (s, 3 H, O=C—Me); 3.60 (s, 2 H, OCH_2); 4.01 (dd, 1 H, *cis*-C=CH); 4.17 (dd, 1 H, *trans*-C=CH); 4.91 (s, 1 H, C=CH—C=O); 6.52 (dd, 1 H, OCH=C); 7.12 (br.s, 1 H, NH)

(to be continued)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}	^1H NMR ($CDCl_3$), δ (J/Hz)
7	1500, 1580, 1600, 1610, 3080, 3200	[a]1.00 (t, 3 H, $CH_2\underline{Me}$); 2.48 (s, 3 H, C=C—Me); 2.67 (s, 3 H, O=C—Me); 3.22—3.85 (m, 4 H, NCH_2, $O\underline{CH_2}Me$); 4.31 (t, 2 H, OCH_2CN); 6.75 (dd, 1 H, C(6)H, ^3J = 8.8, ^4J = 2.2); 7.35 (d, 1 H, C(7)H, ^3J = 8.8); 7.38 (d, 1 H, C(4)H, ^4J = 2.2)
8	1500, 1550, 1600 (C=C—C=O); 3030 (=CH); 3290 (NH)	1.19 (t, 3 H, Me); 1.92 (s, 3 H, C=C—Me); 1.95 (s, 3 H, O=C—Me); 3.46 (m, 6 H, $NC_2H_4OCH_2$); 4.94 (s, 1 H, C=CH—C=O); 10.90 (s, 1 H, NH)
9	1485, 1560, 1600, 1620, 3100, 3200	[a]2.53 (s, 3 H, C=C—Me); 2.71 (s, 3 H, O=C—Me); 6.73 (dd, 1 H, C(6)H, ^3J = 8.6, ^4J = 2.0); 7.32 (d, 1 H, C(7)H, ^3J = 8.6); 7.38 (d, 1 H, C(4)H, ^4J = 2.0)

[a] The ^1H NMR spectrum was recorded in DMSO-d_6.

Synthesis of enamines 3e—g, 6. A solution of acetylacetone **1a** or ethyl acetoacetate **1b** (0.1 mol), vinyloxyalkylamine **2a—c**, **5** (0.1 mol), and benzene (100 mL) was boiled with a Dean—Stark trap until liberation of water ceased. The reaction mixture was cooled, and enamines **3e—g**, **6** were isolated by distillation *in vacuo*.

Preparation of indoles 4a—g, 7 (general procedure). A solution of enamine **3a—g**, **6** (0.1 mol) and 1,4-benzoquinone (0.1 mol) in acetone (100 mL) was boiled for 3 h. After cooling, the precipitated crystals of indoles were separated and recrystallized from EtOH.

The yields and characteristics of the enamines and indoles synthesized are presented in Table 1, and the data of the IR and ^1H NMR spectra are presented in Table 2.

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Received February 28, 1997;
in revised form May 22, 1997