Preparation and properties of the hydroxyindole-3-carboxylic acids[1]

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Received June 5, 1969

A procedure for the synthesis of the 4-, 5-, 6-, and 7-hydroxyindole-3-carboxylic acids starting from the corresponding 4-, 5-, 6-, and 7-benzyloxyindoles respectively has been devised. The benzyloxyindoles are converted to mixtures of their 1- and 3-carbethoxy derivatives by the action of ethyl chloroformate on their Grignard reagents. The hydroxyindole-3-carboxylic acids are then obtained by the alkaline hydrolysis and debenzylation of the benzyloxy-3-carbethoxyindoles.

Canadian Journal of Chemistry, 47, 4375 (1969)

In view of their importance in biology and medicine [cf. review by Cerletti (1)], the metabolism of indole compounds in plants and animals has been the subject of extensive studies in the past. In recent years the importance of the hydroxyindoles (cf. 2, 3), has also been recognized.

Whilst a considerable amount of research has been carried out on the metabolism of 3-indolylacetic acid (cf. 4, 5), very little has been reported on the metabolism of indole-3-carboxylic acid. Acheson and King reported that the urine of rats which had been fed or injected intraperitoneally with indole-3-carboxylic acid, contained the original acid (ca. 20%), the corresponding glucuronide, and 6-hydroxyindole-3-carboxylic acid (6). These authors further reported that oxidation of indole-3-carboxylic acid with a model hydroxylating system (Fe^{2+}, ascorbic acid, EDTA, oxygen) (cf. 7, 8) gave 5- and 6-hydroxyindole-3-carboxylic acid, indole, anthranilic acid, *N*-formylanthranilic acid, and a number of unidentified products. In other instances the oxidation of indole compounds with this system [i.e. indole (9), tryptophan (9) and skatole (10)], has resulted in the formation of all 4 hydroxyindole derivatives, hydroxylated in the benzene moiety of the indole ring, together with other products produced by oxidation of the pyrrole ring.

Before reinvestigating the hydroxylation of indole-3-carboxylic acid, it was desirable to have available authentic samples of the 4-, 5-, 6-, and 7-hydroxyindole-3-carboxylic acids. The synthesis of these 4 compounds is described in this paper.

R_f Values have been reported for both 5- and 6-hydroxyindole-3-carboxylic acids (6, 11, 12), but as far as the authors are aware the unambiguous syntheses of neither these two acids nor the 4- and 7-hydroxyindole-3-carboxylic acids have been reported.

The syntheses of these 4 acids have now been achieved, starting from the corresponding authentic benzyloxyindoles, which are available commercially. Since the reactions of the indole Grignard reagent with both ethyl chloroformate and carbon dioxide [i.e. methods which introduce a COOR group into the 3-position of the indole ring system where R = C_2H_5 or H respectively (cf. 13)] have recently been the subject of extensive studies in these laboratories (14, 15), it was decided to apply one of these methods to the syntheses of the 4-, 5-, 6-, and 7-hydroxyindole-3-carboxylic acids. Preliminary experiments suggested that the route via the ester was the more promising. The benzyloxyindoles were converted into their Grignard reagents and the subsequent reactions with ethyl chloroformate carried out at low temperatures and for relatively short periods of time.

Preliminary thin-layer chromatographic (t.l.c.) analysis of the reaction mixtures indicated that they invariably consisted of mixtures of 3 major components: the benzyloxy-1-carbethoxyindole, the benzyloxy-3-carbethoxyindole, and unchanged starting material. Their presence was confirmed by gas–liquid chromatography (g.l.c.). It was not possible to separate efficiently the reaction mixtures into their individual components by fractional crystallization, but satisfactory separations could be achieved using preparative scale t.l.c.

The reaction between the indole Grignard reagent and ethyl chloroformate proceeded satisfactorily at 0° with the 4-, 5-, and 6-isomers, but was carried out at 20° in the case of the 7-isomer

[1]Issued as NRCC No. 10933.
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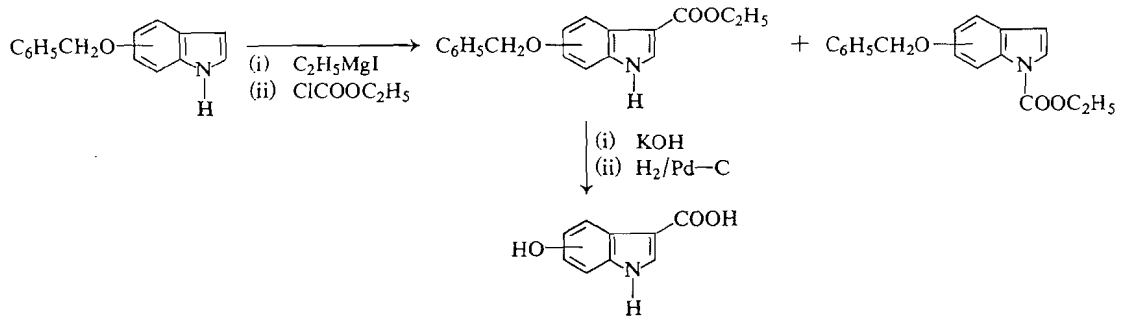


in view of the apparent insolubility of the 7-benzyloxyindole Grignard reagent in the reaction mixture at the lower temperature.

The position of the carbethoxy group in each of the major products was established by their infrared (i.r.) spectra. The carbonyl stretching peak of the 3-esters consistently occurred at lower frequencies (ca. 1670 cm^{-1}) than those of the 1-esters (ca. 1740 cm^{-1}) (cf. 14, 16). The typical N—H stretching peak at 3300–3200 cm^{-1} was also absent in the spectra of the 1-esters. Restricted rotation probably accounts for the fact that two peaks (at 1760 and 1730 cm^{-1}) are observed in the carbonyl region of the i.r. spectrum of 7-benzyloxy-1-carbethoxyindole. The 3-carbethoxy derivatives react slowly with Ehrlich's reagent on heating, whereas the 1-carbethoxy derivatives do not react with this reagent [cf. analogous behavior of 1- and 3-carbethoxyindole with Ehrlich's reagent (14)].

The benzyl group was easily removed from the 4 isomeric benzyloxy-3-carbethoxyindoles hydrogenolytically to give the corresponding 3-carbethoxyhydroxyindoles. The proton magnetic resonance (p.m.r.) spectra of these compounds confirmed that they were in fact substituted in the 3-position. The signals due to the indole 2-protons were observed as singlets (after exchange of the N—H protons with D_2O) at low field, in DMSO-d_6 [cf. Jardine and Brown (17)]. The chemical shifts of these signals and the fact that no significant secondary couplings were observed with any of the protons in the six-membered ring, confirmed that it was the indole 2-proton and not the indole 3-proton that was being observed.

The benzyloxyindole-3-carboxylic acids were readily obtained by hydrolysis of the corresponding benzyloxy-3-carbethoxyindoles with alcoholic potassium hydroxide. However, in the case of the 4-isomer it was impossible to prevent the formation of some decarboxylated product at the same time. In this case the decarboxylation reaction was presumably aided by steric assistance of the 4-benzyloxy group.

The benzyloxyindole-3-carboxylic acids were smoothly debenzylated by catalytic hydrogenation to give the desired hydroxyindole-3-carboxylic acids in high yield. The hydroxyindole-3-carboxylic acids are all high melting colorless crystalline solids, stable in the solid state; 7-hydroxyindole-3-carboxylic acid however, appears to be unstable in solution and is difficult to recrystallize without loss.

Experimental

The melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared, ultraviolet (u.v.), and p.m.r. spectra were recorded on Perkin–Elmer model 237, Beckman DK-2, and Varian A-60-A instruments respectively. The mass spectral data were obtained on a Consolidated Electrodynamics Corp. 21-110B mass spectrometer. A controlled temperature probe was used for introduction of the sample directly into the source.

Benzyloxy-1- and -3-Carbethoxyindoles

Preparation

A solution of the benzyloxyindole[3] (2.2 g, 0.01 moles) in anhydrous ether (50–75 ml) was added dropwise at 5°,[4] during 15–20 min, to the Grignard reagent, prepared from magnesium turnings (0.48 g, 0.02 moles) and ethyl iodide (3.2 g, 0.02 moles) in anhydrous ether (10 ml) (cf. ref. 18). The solution was boiled under reflux for 45 min to complete the formation of the indole Grignard reagent. The solution was cooled to 10°,[5] and ethyl chloroformate (1.2 g, 0.011 moles) added dropwise, with stirring, during 10 min. The resulting reaction mixture was cooled to 0°

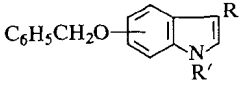
[3]5-Benzyloxyindole was obtained from the Aldrich Chemical Co. and 4-, 6-, and 7-benzyloxyindoles were obtained from the Regis Chemical Co.

[4]Room temperature in the case of 7-benzyloxyindole.

[5]0° in the case of 6-benzyloxyindole.

TABLE I

Experimental data for benzyloxycarbethoxyindoles



Isomer	Grignard reaction products	Melting point (°C)	Yield* (%)	Analyses (%) or *mass measurement on molecular ion:* Found† C	H	N	Spectral data: Infrared‡ (cm^{-1}) 3500–3100	1800–1600	Ultraviolet§ λ_{max} (mμ)
4-	R = $COOC_2H_5$; R′ = H	117–118	40	73.57	5.84	4.77	3235(s);3125(w)	1675(s)	277;[235];208
	R = H; R′ = $COOC_2H_5$	78–80	25	73.55	5.87	4.81	—	1740(s)	[297];289;[257];250;217
5-	R = $COOC_2H_5$; R′ = H	142–144	25	73.11	5.70	4.65	3200(s)	1670(s)	281;238
	R = H; R′ = $COOC_2H_5$	58–59	46	*295.1209*	—	—	—	1740(s)	[305];295;[265];238
6-	R = $COOC_2H_5$; R′ = H	131–132(d)‖	20	73.44	5.76	4.43	3235(s)	1665(s)	[302];274;[228];216
	R = H; R′ = $COOC_2H_5$	Oil	20	*295.1206*	—	—	—	1735(s)	264;[242];[234];229
7-	R = $COOC_2H_5$; R′ = H	166–167	18	73.04	5.93	4.54	3300(s);3140(w)	1665(s)	286;[230]
	R = H; R′ = $COOC_2H_5$	Oil	26	*295.1206*	—	—	—	1760(s);1730(s)	[300];291;[258];250;224

*Starting material (20–37%) was recovered in all cases.
†Calcd. for $C_{18}H_{17}NO_3$ (295.12084): C, 73.22; H, 5.76; N, 4.74.
‡In Nujol; as a thin film for 6- and 7-benzyloxy-1-carbethoxyindole: (s) = strong; (w) = weak.
§In methanol solution; shoulders in parentheses.
‖(d) = With decomposition.

TABLE II

Retention times of compounds present in the Grignard reaction mixtures

Compounds in the reaction mixture	Retention times (min) for isomers			
	4-	5-	6-	7-
Benzyloxyindole	1.58	2.50	2.00	0.42
Benzyloxy-1-carbethoxyindole	3.17	4.67	3.15	0.62
Benzyloxy-3-carbethoxyindole	8.12	14.25	2.48*	4.33

*Isothermal determination at 275°.

and the stirring continued for a further 15 min. The reaction mixture was poured into ice-water and extracted with ether (3 × 50 ml). The combined ether extracts were washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated to dryness *in vacuo*. The reaction products (which contained some unchanged starting material) were separated by preparative t.l.c. Glass plates (100 × 20 cm), coated with silica gel HF-254 (Merck; thickness, 0.9 mm) were used. In the case of the 7-benzyloxy isomer the developing solvent used was benzene – carbon tetrachloride (13:7). In all other cases the plates were developed twice in the same direction with cyclohexane – diisopropyl ether mixtures (a 1:1 mixture was used for the first development and a 4:1 mixture was used for the second run). Under these conditions each plate could initially be loaded with up to ca. 0.5 g of the solid mixture of reaction products. A total of 4 plates was used for each reaction mixture. The separated products were located on the developed chromatoplates by observing them in u.v. light. The bands of silica containing the individual components were scraped from the plates and the products obtained by extraction of the silica with ethanol (300 ml) at room temperature. The filtered ethanol extracts were concentrated to dryness *in vacuo* and the crude products recrystallized from suitable solvents, usually benzene – light petroleum or benzene for the 3-carbethoxy and 1-carbethoxy derivatives respectively. Details of the yields of the products obtained and their physical properties are given in Table I.

Gas–liquid Chromatography

A Varian Aerograph model 204, dual column instrument, fitted with two hydrogen-flame ionization detectors; a 6 ft × 1/8 in. stainless-steel column (5% SE-30 on 60–80 Chromosorb W) was used; the injector and detector temperatures were maintained at 275 and 300° respectively; the nitrogen carrier gas flow rate was 30 ml/min and the hydrogen flow rate was 27 ml/min. The column was maintained at 225° during the determination of the relative retention times of the compounds obtained from the reaction mixture. The values are reported in Table II.

3-Carbethoxyhydroxyindoles

The benzyloxy-3-carbethoxyindole (0.5 g) in methanol (100 ml) was shaken with palladium-on-charcoal (5%; 0.25 g) in a hydrogen atmosphere at room temperature for 1 h. The hydrogenation mixture was filtered through Celite 545 (Fisher) and the filtrate evaporated to dryness *in vacuo*. The crude 3-carbethoxyhydroxyindole so obtained was recrystallized from water containing a small amount of ethanol. The properties of the products are reported in Table III.

Benzyloxyindole-3-carboxylic Acids

A solution of the benzyloxy-3-carbethoxyindole (0.2 g) in a mixture of 1-propanol (30 ml), ethanol (3 ml), and 2 *N* aqueous potassium hydroxide[6] (14 ml) was heated at the temperatures and for the periods specified in Table IV. The solution was then evaporated to small bulk *in vacuo*, diluted with water, extracted with ether (3 × 20 ml), and the ether extracts discarded. The p*H* of the aqueous solution was adjusted to 3 with hydrochloric acid and extracted with ether (3 × 30 ml). The combined, dried (Na_2SO_4) ether extracts were evaporated to dryness *in vacuo* to give the benzyloxyindolecarboxylic acid, which, when recrystallized from aqueous ethanol, had the properties listed in Table IV.

Hydroxyindole-3-carboxylic Acids

A solution of the benzyloxyindole-3-carboxylic acid (0.25 g) in methanol[7] (50 ml) containing a palladium-on-charcoal catalyst (5%; 0.125 g)[8] was shaken in a hydrogen atmosphere at room temperature and under atmospheric pressure for 1 h. The reaction mixture was filtered through Celite 545 (Fisher) and concentrated to dryness *in vacuo*. The crude products were purified by recrystallization from a suitable solvent. The physical properties of the pure compounds and solvent of crystallization are given in Table V.

Thin-layer Chromatography

Glass plates (20 × 20 cm), precoated with silica gel F_{254} (Merck; thickness, 0.25 mm), were used throughout this investigation. The solvent systems used in the separations of the various groups of products and the R_f values of the individual compounds are given in Table VI. The colors given by the compounds with Ehrlich's reagent (after the sprayed plates had been heated at 125° for 10 min) are also reported in Table VI.

Acknowledgments

The authors wish to express their thanks to

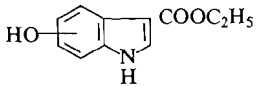
[6]The same quantity of 1 *N* sodium hydroxide solution was used in the case of 4-benzyloxy-3-carbethoxyindole.

[7]A mixture of methanol and ethyl acetate was used to dissolve the 4-isomer.

[8]The catalyst was moistened with water before it was added to the solution to minimize the potential fire hazard.

TABLE III

Experimental data for 3-carbethoxyhydroxyindoles

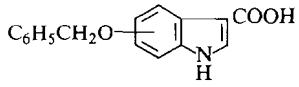


Isomer	Melting point* (°C)	Yield (%)	Analyses (%)† Found C	H	N	Spectral data: Infrared‡ (cm^{-1}) 3500–3100	1800–1600	Ultraviolet§ λ_{max} (mμ) Neutral	Alkaline	p.m.r.‖ 2-proton (τ value)
4-	155–156	68	64.52	5.45	6.73	3300(m);3125(b)	1620(s)	297;235;212	[310];[250]	1.98
5-	185–186	70	64.41	5.65	6.63	3330(b); 3200(b)	1650(s);1625(m)	[300];281;237	325;266;[250];[242]	2.07
6-	174–176(d)	60	64.47	4.92	6.58	3300(b); 3175(b)	1650(s);1625(s)	[304];275;[226]	[318];284;[240]	2.17
7-	188(d)	70	64.59	5.18	6.75	3350(m);3170(b)	1650(s)	292;233;208	317;[241]	2.13

*(d) = With decomposition.
†Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83.
‡In Nujol; (b) = broad; (s) = strong; (m) = medium.
§In methanol; a few drops of 2 *N* potassium hydroxide were added for the measurements in alkaline solution; shoulders in parentheses.
‖In dimethylsulfoxide-d_6. A singlet is observed after the solution has been shaken with D_2O to exchange the N–H protons.

TABLE IV

Experimental data for benzyloxyindole-3-carboxylic acids

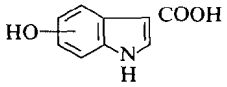


Isomer	Reaction time: Hours at 75°	Days at room temperature	Melting point (°C)	Yield (%)	Analyses (%)* Found C	H	N	Spectral data: Infrared† (cm^{-1}) 3500–3100	1800–1600	Ultraviolet‡ λ_{max} (mμ)
4-	0.5	1	254	75	72.37	5.06	4.94	3130(m)	1680(s)	280;[230];210
5-	5	1	203–204(d)§	90	71.92	4.64	5.12	3370(m)	1665(s)	[305];277;236;213
6-	1	3	185–187(d)§	75	72.10	5.10	5.01	3310(w);3135(m)	1645(s)	[300];[290];273;[230];216
7-	3	1	189–190(d)§	80	71.54	4.67	5.38	3420(m);3380(m)	1660(s)	277;210

*Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.86; N, 5.24.
†In Nujol; (w) = weak; (m) = medium; (s) strong.
‡In methanol solution; shoulders in parentheses.
§(d) = with decomposition.

TABLE V

Experimental data for hydroxyindole-3-carboxylic acids



Isomer*	Melting point** (°C)	Yield (%)	Analyses (%)† Found C	H	N	Spectral data: Infrared‡ (cm^{-1}) 1800–1600	Ultraviolet§: Neutral λ_{max} (ε_{max})	Ultraviolet§: Alkaline λ_{max}
4-	240	85	61.12	3.94	7.76	1625(s);1630(s) (sh)	286(6,925);[235](13,650);211(46,950)	280
5-	187	77	60.85	3.86	7.98	1625(s);1630(s)	[305](6,925);281(8,875);[245](15,250); 237(16,100);213(41,350)	323;[241]
6-	229	70	61.66‖	3.97	7.73	1625(s);1650(s)	[305](5,450);274(8,175); [230](17,700);214(25,200)	312;[280];[235]
7-	230	65	60.95	4.05	7.83	1645(s)	282(5,350);[235](15,025);[208](32,725)	[335];295;[245]

*Solvents of crystallization [isomer(solvent)]: 4-, (ethanol/water); 5-, (benzene/ethanol); 6-, (ethanol/water); 7-, (5% ethanol in water).
†Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91.
‡In Nujol; (s) = strong; (sh) = shoulder. Very broad peaks occur in the OH/NH stretching region (3500–2700 cm^{-1}), probably due to hydrogen bonding in the solid state.
§In 95% ethanol; λ_{max} (mμ); shoulders in square brackets; extinction coefficients in parentheses. A few drops of 2 *N* potassium hydroxide were added for the measurements in alkaline solution.
‖It has proved difficult to obtain a satisfactory microanalytical value for carbon in the case of 6-hydroxyindole-3-carboxylic acid. However, the acid is chromatographically homogeneous and mass measurement of the molecular ion confirms the molecular formula. (Calcd.: 177.0425. Found: 177.0424.)
**With decomposition.

TABLE VI

Thin-layer chromatographic data for indole compounds investigated

Compound name	R_f Values in solvent system*				Color reaction with Ehrlich's reagent
	S_1	S_2	S_3	S_4	
4-Benzyloxyindole	0.44	0.87	0.84	0.71	Blue
4-Benzyloxy-1-carbethoxyindole	0.68	0.89	—	0.60	Colorless†
4-Benzyloxy-3-carbethoxyindole	0.04	0.43	0.53	0.01	Blue
3-Carbethoxy-4-hydroxyindole	—	0.68	0.67	—	Blue
4-Benzyloxyindole-3-carboxylic acid	—	—	0.14	—	Blue
4-Hydroxyindole-3-carboxylic acid	—	—	0.03	—	Blue
5-Benzyloxyindole	0.36	0.87	—	0.61	Purple
5-Benzyloxy-1-carbethoxyindole	0.61	—	—	0.49	Colorless†
5-Benzyloxy-3-carbethoxyindole	0.05	0.58	—	0.02	Mauve
3-Carbethoxy-5-hydroxyindole	0.01	0.42	—	—	Mauve
5-Benzyloxyindole-3-carboxylic acid	0.00	0.19§	—	—	Purple
5-Hydroxyindole-3-carboxylic acid‡	0.00	0.13§	—	—	Purple
6-Benzyloxyindole	0.36	0.90	—	0.61	Violet
6-Benzyloxy-1-carbethoxyindole	0.65	0.96	—	0.55	Colorless†
6-Benzyloxy-3-carbethoxyindole	0.02	0.45	—	0.02	Pale violet
3-Carbethoxy-6-hydroxyindole	—	0.21	—	—	Mauve
6-Benzyloxyindole-3-carboxylic acid	—	0.16	0.35	—	Mauve
6-Hydroxyindole-3-carboxylic acid‡	—	0.17	0.23	—	Blue
7-Benzyloxyindole	0.68	—	0.87	0.84	Violet
7-Benzyloxy-1-carbethoxyindole	0.62	—	0.87	0.45	Pale grey
7-Benzyloxy-3-carbethoxyindole	0.09	—	0.70	0.03	Pale violet
3-Carbethoxy-7-hydroxyindole	—	—	0.20	—	Blue
7-Benzyloxyindole-3-carboxylic acid	—	—	0.15	—	Blue
7-Hydroxyindole-3-carboxylic acid	—	—	0.06	—	Blue

*S_1 = Diisopropyl ether – cyclohexane (1:4); S_2 = diisopropyl ether; S_3 = diisopropyl ether – chloroform (1:1); S_4 = benzene – carbon tetrachloride (13:7).

†A colorless spot on a yellow background was observed.

‡The R_f values of samples of 5- and 6-hydroxyindole-3-carboxylic acid (prepared by the method described above) were determined on paper (ascending development) using both isopropanol – ammonia – water (8:1:1) and *n*-butanol – acetic acid – water (8:2:2) as running solvents. The values obtained (0.26 and 0.20) and (0.76 and 0.73) respectively are comparable to those previously reported in the literature (6, 11, 12).

§A better separation of 5-benzyloxyindole-3-carboxylic acid and 5-hydroxyindole-3-carboxylic acid can be achieved with a diisopropyl ether – dimethylformamide (4:1) solvent system. These two acids have R_f values of 0.32 and 0.12 respectively in the system.

Mr. J. van Ingen for recording the p.m.r. spectra; to Mr. D. J. Embree for recording the mass spectra, and to Dr. W. D. Jamieson for useful discussions of the latter.

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