The Tautomerism and Bromination of Some 1-Hydroxyindole-2-carboxylic Acid Derivatives

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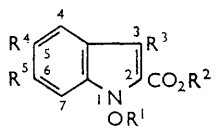
1-Hydroxyindole-2-carboxylic acid with diazomethane gave methyl 1-methoxyindole-2-carboxylate which was attacked by bromine at the 3,5-positions; both the 3,5- and 3,6-dibromo-derivatives were independently synthesised. The n.m.r. spectra suggest that methyl 1-hydroxyindole-2-carboxylate exists as such but 5-bromo-1-hydroxyindole-2-carboxylic acid is present as the 3*H*-indole 1-oxide in deuteriochloroform.

1-Hydroxyindoles have attracted little attention until recently. The chemistry of 1-hydroxy-2-phenylindole, obtained [1] from α-benzoin oxime with concentrated sulphuric acid, is being developed.[2,3] Reissert [4] obtained 1-hydroxyindole-2-carboxylic acid in 1896, and some derivatives were prepared.[5,6] Cypridina luciferin is considered to be a 1-hydroxyindole,[7] and neoglucobrassicin is a 1-methoxyindole derivative.[8]

Claims to have oxidised [9] indole-3-acetic acid to the 1-hydroxy-derivative and to have prepared 1-hydroxyindole from indolemagnesium bromide with hydrogen peroxide [10] have been discounted.[11] This is in agreement with our own unpublished work. 1-Hydroxyindole has recently been obtained by the reductive cyclisation of 2-nitrophenylacetaldehyde.[3]

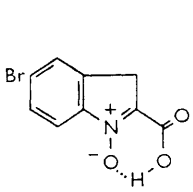
We have now prepared 1-hydroxyindole-2-carboxylic acid (1) by a modification of Reissert's procedure, and with diazomethane, and methanolic sulphuric acid, obtained the derivatives (4) and (2) respectively, while 1-methoxyindole-2-carboxylic acid (3) was formed on



	R^1	R^2	R^3	R^4	R^5
(1)	H	H	H	H	H
(2)	H	Me	H	H	H
(3)	Me	H	H	H	H
(4)	Me	Me	H	H	H
(5)	Me	Me	H	Br	H
(6)	Me	Me	H	H	Br
(7)	Me	Me	Br	Br	H
(8)	Me	Me	Br	H	Br
(9)	H	H	CN	H	H
(10)	Me	Me	CN	Br	H

saponification of the ester (4). The u.v. absorption spectra of these compounds and the bromo-derivative (11) are similar to those of indole-2-carboxylate, and 2,3,3-trimethyl-3*H*-indole 1-oxide [3] so no conclusions concerning the positions of tautomeric equilibria in this solvent can be drawn. The n.m.r. spectra (Table) for the 1-hydroxy-ester (2) and the 1-methoxy-analogue (4) in deuteriochloroform are similar and only the hydroxy-proton is exchanged on adding deuterium oxide. The low-field position of this proton suggested that it is hydrogen-bonded to the adjacent carbonyl group, and the resulting stability accounts for the apparent absence of the 3*H*-indole 1-oxide tautomer.

5-Bromo-1-hydroxyindole-2-carboxylic acid however in deuteriochloroform appears to exist entirely as (11).



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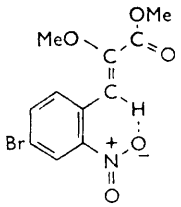

(12)

The n.m.r. spectrum shows no vinylic proton but a methylene group which does not exchange rapidly on adding deuterium oxide while the broad resonance assigned to the carboxyl proton exchanges rapidly. The 7-hydrogen atom has also moved down field with respect to the corresponding atom of the indoles (6), (7) and (8). 1-Hydroxyindole itself exists as 3*H*-indole 1-oxide, while the position of equilibrium for the 2-methyl derivative varies from 0 to 100% of the hydroxy-compound according to the solvent.[3]

Bromination of 1-methoxyindole-2-carboxylic acid (3) gives [4] the 3-bromo-derivative, and we have now found that bromination of the ester (4) caused dibromination. The n.m.r. spectrum of the product (7) showed that bromine atoms were present at position 3, and at position 5 or 6. Both methyl 5- and 6-bromo-1-methoxyindole-2-carboxylates (5) and (6) were synthesised by Reissert's method, from the bromo-2-nitrophenylpyruvic acids followed by methylation with diazomethane, and further bromination of the former gave a product identical with that obtained from methyl 1-methoxyindole-2-carboxylate.

The diazomethane reaction with crude 6-bromo-1-hydroxyindole-2-carboxylic acid gave a second product, identified provisionally as methyl 4-bromo-2-nitro-α-methoxycinnamate (12) from its n.m.r. spectrum. This compound could have been formed by the methylation of some 4-bromo-2-nitrophenylpyruvic acid present in

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the hydroxy-indole. The most interesting feature of the n.m.r. spectrum was the very low field β-proton, presumably deshielded by both the nitro and ester groups. The β-proton of diethyl 2-nitrobenzylidenemalonate (Table) appeared at substantially higher field; perhaps the extra ester group reduces the planarity of the hydrogen-bonded system.

Attempts to induce diethyl 2-nitrobenzylidene malonate [12] to undergo a Michael addition with malonic ester failed although hydrogen cyanide added as described [12] to give diethyl β-cyano-β-2-nitrophenyl-

Nuclear magnetic resonance spectra proton † resonances in τ, J in c./sec. measured at 60 Mc./sec. in deuteriochloroform from tetramethylsilane

Compound *		Ester-methyls
(2)	1-OH, −0·03; [a] 3-H, 3·02; Ar-H(4), 2·3—3·05m	6·12
(4)	1-OMe, 5·80; 3-H, 2·88; Ar-H(4), 2·25—2·95m	6·07
(5)	1-OMe, 5·80; 3-H, 2·98; Ar-H(3), 2·2—2·80m	6·04
(6)	1-OMe, 5·78; 3-H, 2·92; 4-H, 2·48d; 5-H, 2·74q; 7-H, 2·30; [b] $J_{4,5} = 8$; $J_{5,7} = 1·7$	6·05
(7)	1-OMe, 5·80; 4-H, 2·23d; 6-H, 7-H, 2·35—2·65m; $J_{4,6} = 1·5$	6·00
(8)	1-OMe, 5·79; 4-H, 2·13d; 5-H, 2·67q; 7-H, 2·32d; $J_{4,5} = 7$, $J_{5,7} = 1·5$	5·98
(9)	Ar-H(4), 2·05—2·5m; 1-OH and 2-CO_2H, 3·3—4·2 [a]	
(10)	1-OMe, 5·71; 4-H, 2·01d; 6-H, 7-H, 2·25—2·5m; $J_{4,6} = 2$	5·91
(11)	2-CO_2H, −0·40; [a] 3-CH_2, 5·96; 4-H, 2·47; [b] 6-H, 2·40q; [c] 7-H, 1·96d; $J_{4,6} = 2$; $J_{6,7} = 7·5$	
(12)	α-OMe, 6·00; [d] β-H, −2·60; [c] 3-H, 1·02d; 5-H, 2·65q; 6-H, 3·05d; $J_{3,5} = 1·8$; $J_{5,6} = 8·5$	6·02 [d]
(A) [h]	1-Me, 7·43; 3-H, 2·17d; 4-H, 2·53q; [i] 6-H, 2·50 [b]	
(B)	β-H, 1·84; 3-H, 1·82d; [b] Ar-H(3), 2·2—2·7m; $J_{3,4} = 8$	Me, [g] 8·96t; Me, [g] 8·64t; CH_2, [g] 5·89q; CH_2, [g] 5·65q; $J = 7·5$
(C)	3-H, 1·91q; Ar-H(3), 2·1—2·5m; α-H, 5·86d; β-H, 4·61d; $J_{\alpha\beta} = 7$	6·20, 6·25

* A = 5-Bromo-2-nitrotoluene. B = Diethyl 2-nitrobenzylidenemalonate. C = Dimethyl β-cyano-β-2-nitrophenylethane-α,α-dicarboxylate. † Numbers of protons, where necessary, are given in parentheses.

[a] Vanishes on adding D_2O. [b] Shows signs of splitting. [c] Half of the quartet obscured by 4-H resonance. [d] These assignments could be interchanged. [e] Exchanges with added D_2O over 3 weeks. [f] For Me_2SO solution. [g] Ethyl ester. [h] Expected chemical shifts for the aromatic protons calculated from shielding constants,[13] 3-H, 1·99; 4-H, 2·47 and 6-H, 2·47. [i] Low-field half of quartet is under the 6-H resonance.

ethane-αα-dicarboxylate. Cyclisation of this ester (also of the corresponding dimethyl ester) with ethanolic sodium carbonate gave 3-cyano-1-hydroxyindole-2-carboxylic acid (9), and not the ethyl ester as is reported.[12] Bromination of this acid (9) followed by methylation with diazomethane gave 5-bromo-3-cyano-1-methoxyindole-2-carboxylate (10), the position of the bromine being allocated on analogy and also because of the similarity of the n.m.r. spectrum of the compound with that of the indole (7).

EXPERIMENTAL

The instruments used were as described.[14] Infrared spectra are for Nujol mulls and for the 5—7 μ region. Ultraviolet spectra are for methanol (M), or acidified (MA) or basified (MB) methanol and are recorded in mμ, 10^{-4} ε being given in parentheses.

1-Hydroxyindole-2-carboxylic Acid (1).—Redistilled 2-nitrotoluene (87 ml., b. p. 218—220°) and ethyl oxalate (97 ml., b. p. 182—184°) were added to potassium (28 g.) in dry ethanol (47 ml.) and ether (815 ml.). It proved essential to use redistilled reagents and exclude atmospheric moisture. After 6 days at room temperature 2N-aqueous sodium hydroxide (418 ml.) was added, the mixture shaken, and left for 2 hr. The ether layer was separated, extracted with aqueous sodium hydroxide, and the alkaline solutions 2-carboxylic acid (6·7 g.) separated, and after repeated recrystallisation as above had m. p. 159—159·5° (decomp.) on slow heating (lit.,[5] 159·5°) but when placed in a bath at 160° and heated at 4°/min. had m. p. 167—168° (decomp.) (Found: C, 61·1; H, 4·1; N, 7·9. Calc. for $C_9H_7NO_3$: C, 61·0; H, 4·0; N, 7·9%), $\lambda_{max.}$ 2·97, 3·85, 5·90, 6·15, 6·35, 6·48, 6·71, and 6·83 μ, $\lambda_{max.}$ (M) 221infl (1·75), 288 (1·09), and 291 (1·09), $\lambda_{max.}$ (MA) 221infl (1·80), 285 (1·19), and 290 (1·19), $\lambda_{max.}$ (MB) 235infl (1·85), 293 (0·79), 302 (0·74), and 325infl (0·37). Methyl indole-2-carboxylate showed $\lambda_{max.}$ (M) 218 (2·25) and 292 (1·90) mμ.

The acid (1) (1·0 g.) was converted [5] to the methyl ester which had the properties described [5] and showed $\lambda_{max.}$ 3·08 (OH), 5·85, 6·18, 6·54, 6·62, 6·83, and 6·92 μ, $\lambda_{max.}$ (M) 226 (2·16) and 294 (1·66), $\lambda_{max.}$ (MA) 225 (2·16) and 293 (1·74), $\lambda_{max.}$ (MB) 301 (1·00), 310 (1·33), and 358 (0·27).

Methyl 1-Methoxyindole-2-carboxylate (4).—Excess of diazomethane in ether was added to 1-hydroxyindole-2-carboxylic acid (2·0 g.) in ether (50 ml.) and methanol (1 ml.). Next day the solvent volume was reduced to 10 ml. by vacuum evaporation, and cooling to −75° precipitated the ester (1·6 g.) as prisms (from ether–light petroleum, b. p. 40—60°, or methanol), m. p. 64° (lit.,[6] 63—64°) (Found: C, 64·4; H, 5·4; N, 7·0. Calc. for $C_{11}H_{11}NO_3$: C, 64·3; H, 5·4; N, 6·8%), $\lambda_{max.}$ 5·86, 6·24, 6·65, 6·80, and 6·91 μ, $\lambda_{max.}$ (M, MA, and MB) 226 (2·20) and 291 (1·98).

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[14] R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 362.

This ester (4) (1·3 g.) in ethanol (25 ml.) was treated with potassium hydroxide (0·38 g.) in ethanol (10 ml.). Next day ether was added and the precipitated potassium salt collected, dissolved in water, and acidified. 1-Methoxyindole-2-carboxylic acid (1·0 g.) precipitated, needles (from aqueous ethanol), m. p. 183—184° (lit.,[4] 185°) (Found: C, 62·7; H, 4·8; N, 7·3. Calc. for $C_{10}H_9NO_3$: C, 62·7; H, 4·7; N, 7·2%), $\lambda_{max.}$ 3·90br, 5·92, 6·00infl, 6·18, 6·36, 6·50, 6·72, 6·86, and 6·95 μ, $\lambda_{max.}$ (MA) 222infl (2·08) and 290 (1·65), $\lambda_{max.}$ (MB) 286 (1·22).

Methyl 3,5-Dibromo-1-methoxyindole-3-carboxylate (7).—(*a*) Methyl 1-methoxyindole-2-carboxylate (0·48 g.) in glacial acetic acid (3·6 ml.) and water (0·4 ml.) at 5° was stirred and bromine (0·60 g.) in acetic acid (1·5 ml.) added in 3 portions over 15 min. After stirring for 2 hr. at room temperature the mixture was poured onto crushed ice (50 g.), the solid collected and recrystallised (from methanol) to give *methyl 3,5-dibromo-1-methoxyindole-2-carboxylate* (7) (0·6 g.) as needles, m. p. 135·5° (Found: C, 36·5; H, 2·7; Br, 43·8; N, 3·7; OMe, 16·8. $C_{11}H_9Br_2NO_3$ requires C, 36·4; H, 2·5; Br, 44·1; N, 3·9; 2 OMe, 17·1%), $\lambda_{max.}$ 5·68, 6·66, 6·83, 6·90infl, and 6·97 μ.

(*b*) Methyl 5-bromo-1-methoxyindole-2-carboxylate (125 mg.) in acetic acid (0·9 ml.) and water (0·08 ml.) was cooled to 5° and bromine (0·05 ml.) in acetic acid (0·4 ml.) added and the mixture worked up as for (*a*). The dibromo-compound (7) (84 mg.) was obtained, m. p. and mixed m. p. 137—138·5°, i.r. spectra of the specimens from (*a*) and (*b*) identical in the 2·5—15 μ range.

5-Bromo-2-nitrotoluene.—3-Acetamidotoluene was converted into 5-bromo-2-nitrotoluene essentially as described,[15,16] but the intermediate 5-acetamido-2-nitrotoluene, which was shown to be homogeneous by t.l.c., had m. p. 119·5—120° (lit.,[15] 102°).

5-Bromo-2-nitrophenylpyruvic Acid.—5-Bromo-2-nitrotoluene (8·26 g.), ethyl oxalate (freshly redistilled, 5·05 ml.), and sodium (0·88 g.) in dried ethanol (19 ml.) were refluxed for 45 min. and worked up as for the 4-bromo-analogue [17] to give the *pyruvic acid* (4·17 g.) as a pale amorphous solid (from benzene), m. p. 136—146° (decomp.) (Found: C, 37·5; H, 2·1. $C_9H_6BrNO_5$ requires C, 37·6; H, 1·9%).

Methyl 5-Bromo-1-methoxyindole-2-carboxylate (5).—The above pyruvic acid (1·65 g.) was stirred with water (40 ml.), magnesium powder (0·50 g.), and mercuric chloride (12 mg.) for 24 hr., filtered, acidified, and extracted with ethyl acetate (3 × 50 ml.). Evaporation of the dried extract and recrystallisation of the residue from methanol–water (1 : 1 v/v) gave 5-bromo-1-hydroxyindole-2-carboxylic acid as needles (0·6 g.), m. p. 170—175° (decomp.), $\lambda_{max.}$ (M) 234 and 293 mμ. This (0·2 g.) with diazomethane in ether gave methyl 5-bromo-1-methoxyindole-2-carboxylate (0·05 g.), needles (from methanol), m. p. 120—122°, $\lambda_{max.}$ (M) 228 (3·08) and 295 (2·28).

6-Bromo-1-hydroxyindole-2-carboxylic Acid.—4-Bromo-2-nitrophenylpyruvic acid [17] (1·5 g.) was treated with magnesium (0·54 g.), mercuric chloride (11 mg.), and water as for the 5-bromo-isomer and working up as before gave *6-bromo-1-hydroxyindole-2-carboxylic acid* (0·42 g.), which was recrystallised first from toluene then from aqueous methanol to give needles, m. p. 164—180° (decomp.) (Found: C, 40·3; H, 2·6. $C_9H_6BrNO_3,\frac{1}{2}H_2O$ requires C, 40·7; H, 2·6%), $\lambda_{max.}$ 3·00, 5·78, 5·86, 6·19, 6·40, and 6·51 μ.

Methyl 6-Bromo-1-methoxyindole-2-carboxylate (6).—Diazomethane in ether (from *ca.* 2·5 g. nitrosomethylurea) was added to 6-bromo-1-hydroxyindole-2-carboxylic acid (1·0 g.) in ether (25 ml.) and methanol (0·5 ml.) and next day the solvent was removed *in vacuo*. The sticky orange residue was fractionally recrystallised from methanol and gave as the more soluble compound *methyl 6-bromo-1-methoxyindole-2-carboxylate*, m. p. 79—83° (Found: C, 46·5; H, 3·5; Br, 28·2. $C_{11}H_{10}BrNO_3$ requires C, 46·6; H, 3·5; Br, 28·6%), $\lambda_{max.}$ 5·81, 6·21, 6·60, and 6·95 μ. The less soluble compound, needles of m. p. 166—166·5°, was *methyl 4-bromo-2-nitro-α-methoxycinnamate* (Found: C, 42·0; H, 3·3; Br, 25·5; N, 4·5; OMe, 19·3. $C_{11}H_{10}BrNO_5$ requires C, 41·8; H, 3·2; Br, 25·3; N, 4·4; 2 OMe, 19·6%), $\lambda_{max.}$ 5·74, 5·83, 5·91, 6·32, 6·57, and 6·98 μ.

Methyl 3,6-Dibromo-1-methoxyindole-2-carboxylate (8).—The 6-bromo-compound (6) (0·14 g.) was brominated as for the analogue (5) and the product was chromatographed on Kieselgel G silica on a thin-layer plate and developed with ethyl acetate–benzene (1 : 5 v/v). The area between R_F 0·65 and 0·75 which contained the product, now free of starting material, and visible under u.v. light, was extracted with acetone. Evaporation gave *methyl 3,6-dibromo-1-methoxyindole-2-carboxylate* (35 mg.), needles (from methanol), m. p. 119—122° (Found: C, 36·0; H, 2·4. $C_{11}H_9Br_2NO_3$ requires C, 36·4; H, 2·5%), depressed to m. p. 91—125° on mixture with the isomer (7), $\lambda_{max.}$ 5·82, 6·19, 6·68, 6·84, and 6·94infl μ.

Diethyl β-Cyano-β-2-nitrophenylethane-αα-dicarboxylate.—This was obtained in 71% yield as described [12] but had m. p. 55—55·5° (lit.,[12] 46°) (Found: C, 55·9; H, 5·0. Calc. for $C_{15}H_{16}N_2O_6$: C, 56·2; H, 5·0%), $\lambda_{max.}$ 4·43w (CN), 5·73, 5·78, 6·18, 6·29, and 6·53 μ.

Dimethyl β-Cyano-β-2-nitrophenylethane-αα-dicarboxylate.—This was obtained as described for the diethyl ester but using dimethyl 2-nitrobenzylidenemalonate,[18] and was obtained as needles (from methanol), m. p. 88·5—89·5° (Found: C, 53·2; H, 4·4; N, 9·7; OMe, 21·5. $C_{13}H_{12}N_2O_6$ requires C, 53·4; H, 4·1; N, 9·6; 2 OMe, 21·2%), $\lambda_{max.}$ 4·40w (CN), 5·76, 6·18, 6·30, 6·49, and 6·97 μ.

3-Cyano-1-hydroxyindole-2-carboxylic Acid (9).—Diethyl (and dimethyl, which gave lower yields) β-cyano-β-2-nitrophenylethane-αα-dicarboxylate (6·4 g.), water (16 ml.), ethanol (50 ml.), and anhydrous sodium carbonate (6·4 g.) were refluxed for 2 hr., most of the ethanol was removed *in vacuo*, and the residue poured into 2N-aqueous sulphuric acid (100 ml.). 3-Cyano-1-hydroxyindole-2-carboxylic acid (3·66 g.) precipitated, yellow needles (from water), m. p. 195—198° (decomp.) (lit.,[12] 211°) (Found: C, 59·6; H, 3·1; N, 13·7. Calc. for $C_{10}H_6N_2O_3$: C, 59·4; H, 3·0; N, 13·9%), $\lambda_{max.}$ 3·18 (OH), 3·82 (OH), 4·47 (CN), 5·89, 5·94, 6·49, 6·59, and 6·92 μ.

Methyl 5-Bromo-3-cyano-1-methoxyindole-2-carboxylate (10).—The above acid (11) (0·38 g.) in acetic acid (3·3 ml.) and water (0·36 ml.) at 5° was treated with bromine (0·22 ml.) in acetic acid (1·5 ml.), stirred for 2 hr., and poured onto crushed ice (50 g.). The precipitate (0·4 g.) was collected, dried, and in ether (15 ml.) and methanol (0·3 ml.) was treated with excess of diazomethane. Next day the solvent was evaporated and the residue gave *methyl 5-bromo-*

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3-*cyano*-1-*methoxyindole*-2-*carboxylate* (10), buff crystals (from methanol), m. p. **143**—**157°** (Found: C, **46·3**; H, **2·9**. $C_{12}H_9BrN_2O_3$ requires C, **46·6**; H, **2·9**%), $\lambda_{max.}$ **4·50** (CN), **5·78**, **6·61**, and **6·87** μ.

Methyl **4**-*Cyano*-1,2-*dihydro*-1-*hydroxy*-2-*oxoquinoline*-3-*carboxylate*.—Dimethyl β-cyano-β-2-nitrophenylethane-αα-dicarboxylate was refluxed for **1½** hr. with sodium (**0·14** g.) dissolved in methanol (20 ml.), the solvent was evaporated, 2N-aqueous sulphuric acid (10 ml.) added, and after 12 hr. at 0° the precipitate (**1·09** g.) was collected. It recrystallised to give the *methyl ester*, yellow needles (from methanol–water), m. p. **193·5**—**194·5** (sealed tube) (Found: C, **57·0**; H, **3·6**; N, **11·1**; OMe, **12·9**. $C_{12}H_{10}N_2O_4,\frac{1}{2}H_2O$ requires C, **56·9**; H, **3·6**; N, **11·1**; OMe, **12·2**%), $\lambda_{max.}$ **3·20**, CN absorption not observed, **5·79**, **6·10**, **6·21**, **6·30**, **6·48**, and **6·87** μ; the corresponding ethyl ester has been similarly obtained [12] using different bases.

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