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The first entry to 5,6-dihydroxy-3-mercaptoindole, 5-hydroxy-3-mercaptoindole and their 2-carbomethoxy derivatives by a mild thiocyanation/reduction methodology

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Abstract—The hitherto unknown 5,6-dihydroxy-3-mercaptoindole (**4a**) and its 2-carbomethoxy derivative (**4b**), as well as the analogous 5-hydroxy 3-mercaptoindoles, have been conveniently obtained as *O*,*S*-acetyl derivatives **3a**–**d** by thiocyanation of the corresponding acetoxyindoles **1a**–**d** with the NH_4SCN/oxone system followed by SmI_2 reduction and acetylation.

The 5,6-dihydroxyindoles constitute a peculiar group of naturally occurring catecholic indoles which play a central role in the biosynthesis of eumelanins, the characteristic dark pigments of skin, hair, eyes and melanomas.[1] Besides their biological importance in human pigmentation,[2] interest in the 5,6-dihydroxyindoles derives from their increasing applications in cosmetics[3] and medicinal chemistry, for example, as active moieties in antiviral agents and antibiotics.[4] More recently, advances in materials science have opened new horizons for 5,6-dihydroxyindoles and polymers thereof,[5] for example, in the fields of organic conductors and photon harvesting systems.[5b]

The preparation of 5,6-dihydroxyindoles is notoriously difficult, due to their marked facility to oxidation with formation of dark polymeric materials, and most of the available procedures provide access, in fact, to their *O*-acetyl derivatives, for example, 5,6-diacetoxyindole (**1a**).[6] 5,6-Diacetoxyindoles are commonly used as storable and ready sources of 5,6-dihydroxyindoles because they can be hydrolysed in situ, for example, for studies on eumelanin formation and structure, thus avoiding handling of the unstable *o*-diphenol.

Recently, as a part of a research programme aimed at exploiting 5,6-dihydroxyindoles as basic structural units for new molecular scaffolds and bioinspired materials, we required access to derivatives bearing a thiol group on the 3-position of the indole ring. A number of methodological and experimental issues, central to the realisation of this goal, were immediately apparent, that were raised by the presence of an additional oxidisable group on the 5,6-dihydroxyindole skeleton. Several indole-3-thiols have been described in the literature, but most of the reported methodologies[7] for the introduction of the sulfur substituent could not be extended to oxidisable substrates bearing sensitive functionalities such as the 5,6-diacetoxyindoles.

We report herein, a convenient access route to the hitherto unknown 3-mercapto derivatives of 5,6-dihydroxyindoles and the extension of this methodology to the preparation of the 5-hydroxy analogues, which provide the core structures of a number of bioactive compounds.[8] The synthetic plan (Scheme 1) relies upon thiocyanation of 5,6-diacetoxyindoles and 5-acetoxyindoles **1a**–**d**[9] as a means to install a sulfur on the 3-position of the indole ring. A reductive step then furnishes the SH group, which is eventually protected by acetylation, to give the desired products.

Thiocyanation of **1a**–**d** was successfully carried out with the recently developed NH_4SCN/oxone system,[10a] and afforded the desired 3-thiocyano derivatives **2a**–**d** in good yields (75–90%) (Table 1).[11] The NH_4SCN/oxone

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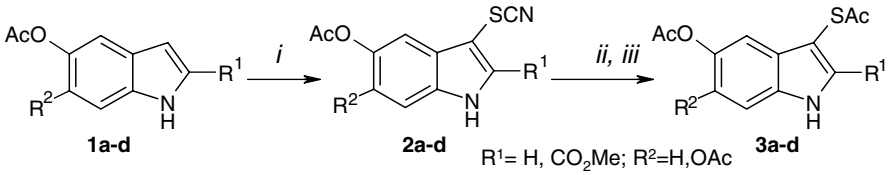


Scheme 1. Synthesis of acetoxy-3-acetylthioindoles. Reagents: (i) NH_4SCN/oxone, molar ratio 1:1.2; (ii) SmI_2; (iii) Ac_2O, overnight.

Table 1. Thiocyanation of **1a–d** to **2a–d**

1	R^1	R^2	Solvent, rxn time	2 Yield[a] (%)
a	H	OAc	MeOH, 2 h	90
b	CO_2Me	OAc	CH_3CN, 24 h	82
c	H	H	MeOH, 2 h	85
d	CO_2Me	H	CH_3CN, 24 h	80

[a] Isolated yields.

Table 2. Reduction of thiocyanates **2a–d** to thiolesters **3a–d**

2	R^1	R^2	SmI_2 (eqs.)[a]	3 (% yield)[b]
a	H	OAc	2.5	78
b	CO_2Me	OAc	4.3	74
c	H	H	2.5	75
d	CO_2Me	H	4.3	75

[a] Two additional eqs were added when necessary following TLC detection of partially reduced species.
[b] Isolated yields.

methodology[10a] is mild and proved to be convenient with respect to other methods which required harsher treatments.[10b–d] It has been described for indole itself and a number of simple derivatives, including 5-methoxyindole, but has not yet been extended to acetoxyindoles and indole-2-carboxylates. Sulfur substitution at the 3-position of indole-2-carboxylates is not an easy task and has been achieved using various forms of electrophilic sulfur reagents, including disulfides and sulfenyl chlorides, but only few are sufficiently mild and tolerant of a wide range of indole substrates.[12] The present demonstration that 2-carbomethoxyacetoxyindoles can be thiocyanated by the NH_4SCN/oxone system extends the scope of this methodology and is an interesting result per se considering also the value of the thiocyanate group as a versatile precursor of sulfur functionalities.[13] In the case of **1b** and **1c** acetonitrile was used in place of methanol as this latter induced deacetylation of the substrates. Mechanistically, the reaction has been suggested[10a] to involve the initial oxidation of the indole to a radical cation which would then be attacked by the SCN^- anion at the 3-position. The presence of the electron-withdrawing 2-carbomethoxyl group deactivates the substrate to oxidation and, indeed, **1b/d** reacted at much slower rate than **1a/c** so that a chromatographic step was required to remove starting material and minor side products.

Once the thiocyano group was installed, we next sought a mild reductive procedure for obtaining the SH group. Survey of the literature suggested that SmI_2 could aptly serve this scope[14] and, indeed, all thiocyano derivatives **2a–d** were reduced to the corresponding thiols in satisfactory yields (Table 2). The reaction was carried out by modification of previously described procedures.[14a] O,S-acetylated products **3a–d**[15] could be safely isolated and stored without appreciable oxidation/decomposition. Protection of the carboxyl group as methyl ester (**1b** and **1d**) was critical for the success of the thiocyanation and reduction steps, since all attempts to convert the corresponding free acids met with failure.[16]

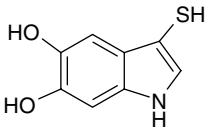
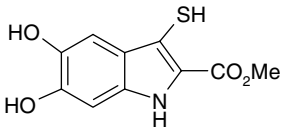
The conversion of **2a–d** to **3a–d** described in this Letter extends the scope of the SmI_2-based reduction to indole thiocyanates bearing ester functionalities. These results underscore the compatibility of SmI_2 with base-sensitive groups, a critical requirement for the preparation of **3a–d** since the early methods, involving refluxing with 2.5 N NaOH[10c] or hydride reagents[17] were clearly inapplicable.

In a separate set of experiments we briefly assessed whether **3a** and **3b** could be safely de-acetylated to the corresponding 5,6-dihydroxy-3-mercaptoindoles. Accordingly, a procedure was devised in which an acetone solution of **3a** or **3b** was carefully added under argon to 0.1 M phosphate buffer, pH 12. Excess $Na_2S_2O_4$ was then added, the pH was rapidly brought to 3 with HCl, and the solution was then extracted with ethyl acetate to give pure 5,6-dihydroxy-3-mercaptoindole (**4a**) and 2-carbomethoxy-5,6-dihydroxy-3-mercaptoindole (**4b**). As expected, both indoles proved difficult to handle due to their marked tendency to oxidation giving dark materials in solution and even when stored dry in the cold. However, by operating under controlled conditions with the rigorous exclusion of oxygen it was possible to provide spectral characterisation of both 5,6-dihydroxy-3-mercaptoindole and its 2-carbomethoxyl derivative[18] (Table 3).

Compounds **4a**,**b** were thiolic in character, as deduced from SH signals in the proton spectra and the ^{13}C NMR chemical shifts indicating in both cases eight aromatic ring signals in the sp^2 carbon region. Moreover, the COSY spectrum of 5,6-dihydroxy-3-mercaptoindole in acetone-d_6 revealed that the H-2 proton was coupled both to the NH and SH protons, whilst the HMBC spectrum indicated cross peaks of the SH proton with both C2 and C3 carbons. In 2-carbomethoxy-5,6-dihydroxy-3-mercaptoindole, the SH signal was shifted downfield by ca. 2 ppm, due probably to the electron-withdrawing effect of the COOMe group and/or intramolecular hydrogen bonding.[19]

In conclusion, we have described the first access route to the novel, highly unstable 3-mercapto derivatives of 5,6-dihydroxyindole by a mild thiocyanation/reduction

Table 3. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data ($(CD_3)_2CO$) for 5,6-dihydroxy-3-mercaptoindole (**4a**) and 2-carbomethoxy-5,6-dihydroxy-3-mercaptoindole (**4b**)[a]

Position	 **4a**		 **4b**	
	^{1}H (multiplicity, J, Hz)	^{13}C	^{1}H (multiplicity, J, Hz)	^{13}C
N–H	10.02 (br s)		10.43 (br s)	
S–H	3.09 (d, $J = 1.6$)		4.92 (s)	
OH	7.81 (br s), 7.74 (br s)		8.23 (br s), 8.37 (br s)	
2	7.16 (dd, $J = 2.4$, 1.6)	127.3		130.5
3		94.8		113.2
3a		123.4		120.3
4	7.03 (s)	103.1	6.98 (s)	103.2
5		141.1		142.1
6		143.4		147.6
7	6.89 (s)	97.4	6.92 (s)	97.0
7a		131.1		132.2
CO	—	—		162.0
OMe	—	—	3.85 (s)	50.4

[a] Resonances have been assigned on the basis of COSY; HMQC and HMBC experiments.

methodology that has been successfully extended to 5-hydroxyindole and the 2-carbomethoxy derivatives. A complete spectral characterisation of the 5,6-dihydroxy-3-mercaptoindoles has also been provided for the first time. These results represent an important advance in the chemistry of hydroxyindoles since no thiol-containing derivative of this class of heterocycles has been described so far. 5,6-Dihydroxy-3-thioindoles and their analogues may find interesting applications in material sciences and may also provide valuable scaffolds for a variety of compounds with potential biological and pharmacological properties, for example, for the treatment of HIV,[20] as anti-allergy[21] and antianginal agents,[22] as inhibitors of tubulin polymerisation[23] and for the development of complex heterocyclic systems such as heteroaryl-fused bioactive 5-oxo-1,4-thiazepine-3-carboxamides.[24]

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9. Compounds **1a**–**d** were prepared by acetylation of the corresponding hydroxyindoles obtained either commercially (for **1c** and **1d**) or by known procedures (for **1a** and **1b**).[25] Esterification of carboxyl groups to obtain **1b** and **1d** was readily achieved by treatment of the acetylated derivatives with diazomethane in cold ether for 30 min.
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11. Thiocyanation of **1a**–**d** was carried out essentially as in Ref. 10a (see also Table 1). Briefly, a solution of the indole (0.1 M) and ammonium thiocyanate was stirred with oxone at rt. After complete substrate consumption (TLC, eluant: cyclohexane/AcOEt 55:45) the mixture was quenched with water and the precipitate collected by filtration and washed with cold water was found to consist of the crude thiocyanate which was not further purified in the case of **2a** and **2c** or was fractionated by PLC (eluant cyclohexane/ethyl acetate 1:1) in the case of **2b** and **2d**. Compound **2a**: amorphous solid, ESI(+)-MS $m/z = 291$ $[M+H]^+$; ESI-HRMS calculated for $C_{13}H_{11}N_2O_4S$ 291.0439 $[M+H]^+$, found 291.0470; UV λ_{max} (MeOH) 281 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (3H, s, $OCOCH_3$), 2.37 (3H, s, $OCOCH_3$), 7.16 (1H, s), 7.29 (1H, d, $J = 2.8$ Hz), 7.39 (1H, s, H-4), 8.86 (1H, s, N–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.5, 21.7 ($2 \times OCOCH_3$), 91.9 (C), 100.4 (C), 108.5 (CH), 112.2

(C), 112.9 (CH), 126.0 (C), 134.2 (CH), 138.2 (C), 139.6 (C), 170.7, 171.0 ($2\times OCOCH_3$). Compound **2b**: ESI(+)-MS $m/z = 349$ $[M+H]^+$; ESI-HRMS calculated for $C_{15}H_{13}N_2O_6S$ 349.0494 $[M+H]^+$, found 349.0506; UV λ_{max} (MeOH) 304 nm; ^1H NMR (CD_3OD) δ (ppm): 2.30 (3H, s, $OCOCH_3$), 2.31 (3H, s, $OCOCH_3$), 4.01 (3H, s, COOMe), 7.40 (1H, s, H-7), 7.68 (1H, s, H-4); ^{13}C NMR (CD_3OD) δ (ppm) 21.0 ($2\times OCOCH_3$), 53.9 (OCH_3), 96.3 (C), 109.1 (CH), 112.2 (C), 114.7 (CH), 126.5 (C), 127.3 (C), 135.2 (C) 140.3 (C), 143.5 (C), 163.0 (C), 170.6 ($OCOCH_3$), 171.0 ($OCOCH_3$). Compound **2c**: ESI(+)-MS $m/z = 233$ $[M+H]^+$; ESI-HRMS calculated for $C_{11}H_9N_2O_2S$ 233.0385 $[M+H]^+$, found 233.0390. UV λ_{max} (MeOH) 274 nm; ^1H NMR (400 MHz, CD_3OD) δ (ppm): 2.31 (3H, s, $OCOCH_3$), 7.01 (1H, dd, $J = 8.6$, 2.2 Hz), 7.41 (1H, dd, $J = 2.2$, 0.6 Hz), 7.48 (1H, dd, $J = 8.6$, 0.6 Hz), 7.76 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 21.9 (–$OCOCH_3$), 92.8 (C), 98.8 (C), 112.2 (CH), 113.7 (C), 115.0 (CH), 119.7 (CH), 131.2 (C), 135.6 (CH), 148.0 (C), 172.9 ($OCOCH_3$). Compound **2d**: ESI(+)-MS $m/z = 291$ $[M+H]^+$; ESI-HRMS calculated for $C_{13}H_{11}N_2O_4S$ 291.0439 $[M+H]^+$, found 291.0390; UV λ_{max} (MeOH) 300 nm; ^1H NMR (400 MHz, CD_3OD) δ (ppm): 2.31 (3H, s), 4.00 (3H, s), 7.14 (1H, dd, $J = 9.0$, 2.2 Hz), 7.51 (1H, d, $J = 9.0$ Hz), 7.54 (1H, d, $J = 2.2$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 23.2 ($COCH_3$), 54.2 (OCH_3), 97.2 (C), 114.0 (CH), 115.0 (C), 116.4 (CH), 123.7 (CH), 126.9 (C), 130.7 (C), 135.7 (C), 148.9 (C), 162.4 ($OCOCH_3$), 173.0 ($OCOCH_3$) Purity (>95%) of all products obtained in Table 1 was demonstrated by ^1H NMR.

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15. Reduction of thiocyanates **2a**–**d** was carried out as follows (see also Table 2). A 0.1 M SmI_2 solution in dry THF (2.5 equiv) was added to a solution of the appropriate thiocyanate in the same solvent at rt under an argon atmosphere. After few minutes the colour of the mixture turned from blue to yellow and the progress of the reaction was monitored by TLC analysis. When necessary a further amount of SmI_2 was added to ensure completion of the reduction which was observed over a period of 2–6 h. The mixture was then treated with excess acetic anhydride, left under stirring overnight and extracted 3 times with ethyl acetate. The organic phases were washed with an aqueous solution of potassium carbonate and potassium sodium tartrate (1:10 w/w). After evaporation to dryness the residue was purified by silica gel column chromatography (eluant cyclohexane/ethyl acetate 1:1) to give the desired thioacetate. Compound **3a**: off-white solid, ESI(+)-MS $m/z = 308$ $[M+H]^+$; ESI-HRMS calculated for $C_{14}H_{14}NO_5S$ 308.0593 $[M+H]^+$, found 308.0570; UV λ_{max} (MeOH) 270, 296 nm; ^1H NMR ($(CD_3)_2CO$) δ (ppm): 2.26 (6H, s, $OCOCH_3$), 2.35 (3H, s, $SCOCH_3$), 7.26 (1H, s), 7.37 (1H, s), 7.56 (1H, d, $J = 2.8$ Hz), 10.75 (1H, br s); ^{13}C NMR ($(CD_3)_2CO$) δ (ppm): 20.23, 20.80 ($2\times OCOCH_3$) 29.80 ($SCOCH_3$), 99.4 (C), 107.1 (CH), 112.5 (CH), 127.2 (C), 133.2 (CH), 134.3 (C), 138.1 (C), 139.6 (C),168.8, 168.9 ($2\times OCOCH_3$), 195.4 ($SCOCH_3$). Compound **3b**: ESI(+)-MS $m/z = 366$ $[M+H]^+$; ESI-HRMS calculated for $C_{16}H_{16}NO_7S$ 366.0647 $[M+H]^+$, found 366.0700; UV λ_{max} (MeOH) 304 nm; ^1H NMR (CD_3OD) δ (ppm): 2.28 (6H, s, $OCOCH_3$), 2.40 (3H, s, $SCOCH_3$), 3.90 (3H, s, COOMe) 7.33 (1H, s), 7.34 (1H, s); ^{13}C NMR (CD_3OD) δ (ppm): 21.4 ($2\times OCOCH_3$), 30.6 ($SCOCH_3$), 53.47 ($COOCH_3$), 97.5 (C), 109.0 (CH), 115.6 (CH), 129.2 (C), 132.16 (C), 135.6 (C), 140.4 (C), 143.7 (C), 162.9 (*C*OOMe), 171.2, 171.6 ($2\times OCOCH_3$), 196.4 ($SCOCH_3$). Compound **3c**: ESI(+)-MS $m/z = 250$ $[M+H]^+$; ESI-HRMS calculated for $C_{12}H_{12}NO_3S$ 250.0538 $[M+H]^+$, found 250.0590. UV λ_{max} (MeOH) 285 nm ^1H NMR (400 MHz, CD_3OD) δ (ppm): 2.31($3H\times 2$, s, $COCH_3$), 7.00 (1H, dd, $J = 8.2$, 1.8 Hz), 7.40 (1H, d, $J = 1.8$ Hz), 7.47 (1H, d, $J = 8.2$ Hz), 7.54 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm):. 21.8 ($OCOCH_3$), 31.6 ($SCOCH_3$), 98.2 (C), 112.2 (CH), 115.0 (CH), 119.7 (CH) , 130.1 (C), 134.9 (C), 135.6 (CH) , 148.3 (C), 172.9 ($OCOCH_3$), 196.4 ($SCOCH_3$). Compound **3d**: ESI(+)-MS $m/z = 308$ $[M+H]^+$; ESI-HRMS calculated for $C_{14}H_{14}NO_5S$ 308.0593 $[M+H]^+$, found 308.0620; UV λ_{max} (MeOH) 299 nm; ^1H NMR ($(CD_3)_2CO$) δ (ppm): 2.29 (3H, s, $OCOCH_3$), 2.44 (3H, s, $SCOCH_3$), 3.92 (3H, s, COOMe), 7.25 (1H, dd, $J = 8.8$, 2.4 Hz), 7.31 (1H, d, $J = 2.4$ Hz), 7.67 (1H, d, $J = 8.8$ Hz); ^{13}C NMR ($(CD_3)_2CO$) δ (ppm): 20.9 ($OCOCH_3$), 30.3 ($SCOCH_3$ shoulder of the solvent signal), 52.3 ($COOCH_3$), 95.9 (C), 113.1 (CH), 114.4 (CH), 121.6 (CH), 130.7 (C), 131.1 (C), 134.7 (C), 146.8 (C), 160.8 (*C*OOMe), 170.1 ($OCOCH_3$), 192.3 ($SCOCH_3$). Purity (>95%) of all products obtained in Table 1 was demonstrated by ^1H NMR.
16. Thiocyanation of the free acid (**1b**; $R^1 = CO_2H$) resulted in a quite complex mixture in which the main product was 2-carboxy-5,6-dihydroxy-3-thiocyanoindole (probably the deacetylation occurred because of the methanol in the acid medium due to the oxone). Moreover, in the next step, the work up of the reduction mixture also suffered of serious yield decrease probably because of the formation of samarium-carboxyindole complexes difficult to destroy even by treating with a tartrate solution.[15]
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