Metal hydride mediated reduction of 3-(alkylthio)oxindoles containing other potentially reducible groups

Terrence J. Connolly and Tony Durst

Abstract: The reduction of several 3-(methylthio)oxindoles bearing ester groups on the benzene ring has been studied. The reaction is very dependent on the substitution of the oxindole, and the position of the ester group. Deprotonation of the C3 center by the metal hydride is the major initial pathway. This deprotonation plays a role in the reduction of the pendant ester group. Ester groups *ortho*, and presumably *para*, to C3 are very difficult to reduce, reaction only occurring with excess $LiAlH_4$ at elevated temperatures. Once reduction starts, it is very difficult to stop, with reduction of the ester to a methyl group being observed. When deprotonation at this center is blocked, ester reduction becomes straightforward and can be accomplished at room temperature with $LiEt_3BH$.

Key words: oxindole, reduction, anion.

Résumé : On a étudié la réduction de plusieurs 3-(méthylthio)oxindoles portant des groupes esters sur le noyau benzénique. La réaction varie grandement suivant la nature et la position du substituant présent sur l'oxindole. La déprotonation du centre C3 par l'hydrure métallique est le principal chemin réactionnel initial. Cette déprotonation joue un rôle important dans la réduction du groupe ester. Il est très difficile de réduire les groupes esters *ortho*, et probablement *para*, par rapport au centre C3; la réaction ne se produit qu'avec du $LiAlH_4$, à températures élevées. Lorsque la réduction est induite, il est difficile de l'arrêter; on observe alors la réduction de l'ester en groupe méthyle. Lorsqu'on bloque la déprotonation de ce centre, la réduction de l'ester redevient normale et on peut la réaliser à la température ambiante avec du $LiEt_3BH$.

Mots clés : oxindole, réduction, anion.

[Traduit par la rédaction]

Introduction

The chemistry of oxindoles continues to attract considerable attention, possibly due to the biological activity of substituted oxindoles (1). Given the importance of these molecules, studies of fundamental reactions will lead to a greater understanding of their reactivity, and will be of general interest to those planning multistep syntheses.

Although the reaction of oxindole with $LiAlH_4$ has been known for quite some time, there is little mention in the literature of metal hydride reductions of oxindoles bearing other potentially reducible groups. Julian and Printy reported the reduction of 1-methyloxindoles to form 1-methylindoles and indolines with $LiAlH_4$ (2). This group also noted that oxindoles that were not substituted on nitrogen were not reactive towards $LiAlH_4$. Other studies supported these findings or showed that very little reduction occurs (3, 4). Based on numerous other studies, the conclusion was reached that oxindoles having a single 3-substituent undergo $LiAlH_4$ reduction to afford indoles whereas 3,3-disubstituted oxindoles are reduced to indolines when the reductions are carried out in refluxing dioxane (5–8). Nishio et al. have recently reexamined some of this chemistry, and the use of Dibal-H as a reducing agent (9). Their findings suggest that N-unsubstituted oxindoles, regardless of further substitution, are not reduced with Dibal-H. In addition, when reduction with Dibal-H occurred, indoles rather than indolines were obtained as the major products. Although a comprehensive study was conducted, very little speculation was made regarding the mechanism.

Even less is known regarding the mechanism of metal hydride mediated reductions of oxindoles carrying other potentially reducible groups. Brossi and co-workers, in a series of publications, showed that the nitrile group of 1,3,3-trisubstituted oxindoles with cyanomethyl groups at the 3 position could be reduced without reaction at the oxindole carbonyl (10–12). Pierce et al. studied in detail the reduction of 3-(methylene)oxindoles with $NaBH_4$ (13). Plieninger and Allen examined the reductions of oxindoles with borane (14, 15). To the best of our knowledge, there have not been any studies on the reduction of oxindoles that have pendant ester groups on the benzene ring. In the course of research in our laboratory, we recently had the opportunity to study this reaction in detail. An explanation of these results, and an extension to generalize such reductions by employing several isomers and various reduction conditions, is the subject of this paper.

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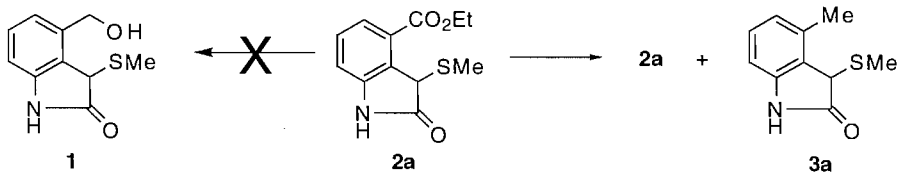
Scheme 1.



Results

Recent synthetic studies in our laboratory required an efficient synthesis of oxindole **1**. Due to the literature precedent arguing that reduction of the oxindole carbonyl with metal hydrides is difficult when the oxindole has a free N-H, we believed that reduction of the pendant ester group of **2a** would afford the desired 4-hydroxymethyl group. Due to the pioneering work of Gassman and van Bergen (16, 17), oxindoles with the desired framework as shown in **2a** are available in a one-pot synthesis from substituted anilines via a rearrangement of the intermediate aza-sulfonium salts. Oxindole **2a** was prepared from ethyl (3-amino)benzoate in a yield consistently above 75%. However, reduction of **2a** with up to five equivalents of Dibal-H in THF returned starting material in a quantitative yield. Likewise, use of other reducing agents like $LiBH_4$, $LiEt_3BH$, Red-Al, and even $LiAlH_4$ in THF at room temperature resulted in the recovery of starting material. When more forcing reduction conditions were used (10 equivalents $LiAlH_4$, refluxing THF, 18 h), a 1:1.2 mixture of starting material and the completely reduced product **3a** was obtained.

In an attempt to gain more mechanistic insight into these results, a systematic study of various related isomers and analogs of **2** was undertaken. All of the desired starting oxindoles were prepared via Gassman's method (16, 17), or via the modified Gassman method reported by Wierenga et al. (18). All of the substrates in this paper were screened under two different reduction conditions: the reaction with $LiEt_3BH$ was done in THF at room temperature whereas reduction with $LiAlH_4$ was done in refluxing THF. Shown in Table 1 are the results from a series of reductions.

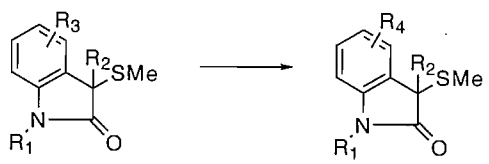


Table 1. Summary of reduction results for oxindoles **2a–2d**.

Entry	R_1	R_2	R_3	R_4	Yield	Conditions[a]
a	H	H	4-CO_2Et	4-CO_2Et	>95%	A
a	H	H	4-CO_2Et	4-CH_3	90%[b]	B
b	Me	H	4-CO_2Et	4-CH_3	90%	B
c	H	Me	6-CO_2Et	6-CH_2OH	88%	A[c]
d	H	H	7-CO_2Et	7-CH_2OH	~84%	A,B[c]

[a]A: $LiEt_3BH$, THF, RT; B: $LiAlH_4$, THF, Δ.
[b]Based on recovered starting material.
[c]Could not be reduced further on exposure to conditions B.

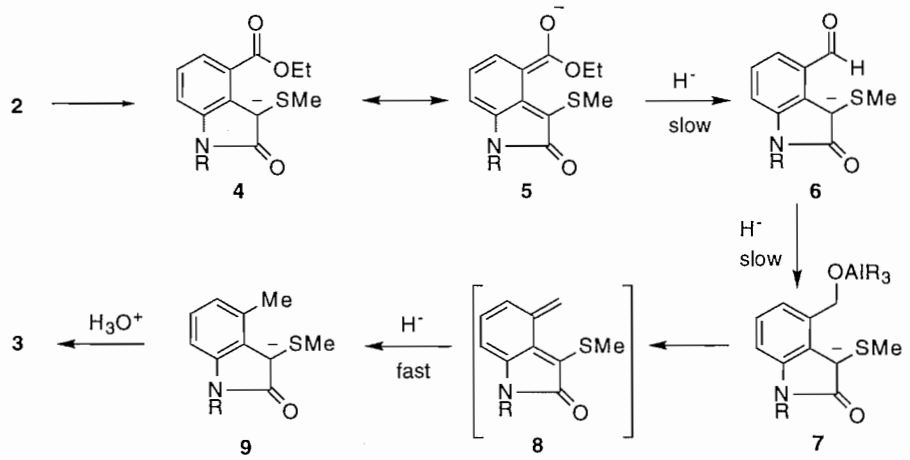
Examination of the table shows a number of trends. Under both $LiEt_3BH$ and $LiAlH_4$ reduction conditions, the oxindole carbonyl group was quite inert to reduction (typically, less than 5% of the product mass was composed of indole and indoline products). It is also evident from substrates **2a** and **2b** that, for oxindoles having a proton on C3 and the ester group *ortho* to this position, initial reduction of the ester group is quite difficult. However, in both cases, once reduction is initiated, it is difficult to stop at the benzylic alcohol stage. For both substrates, which differed only in the N-methyl group, reduction did not occur until excess $LiAlH_4$ was used and the reaction mixture was exposed to harsh conditions, i.e., refluxing THF for prolonged periods of time.

In the case of substrate **2c**, the oxindole was methylated at C3 and had the ester group *para* to C3. Reduction proceeded smoothly with both $LiEt_3BH$ and $LiAlH_4$ to afford the benzylic alcohols. Isolation of the alcohol and its exposure to the forcing conditions ($LiAlH_4$, THF, Δ) resulted in the recovery of starting material. Similarly oxindole **2d**, which was not methylated at C3 and had the ester group *meta* to C3, was also smoothly reduced to the benzylic alcohol with both $LiEt_3BH$ at room temperature and $LiAlH_4$ in refluxing THF. Again, isolation of the benzylic alcohol **3d** and attempted further reduction with $LiAlH_4$ in refluxing THF did not lead to further reduction of the alcohol. Instead, reduction of the oxindole carbonyl group occurred, although this was only about 5% of the mass balance even after 12 h.

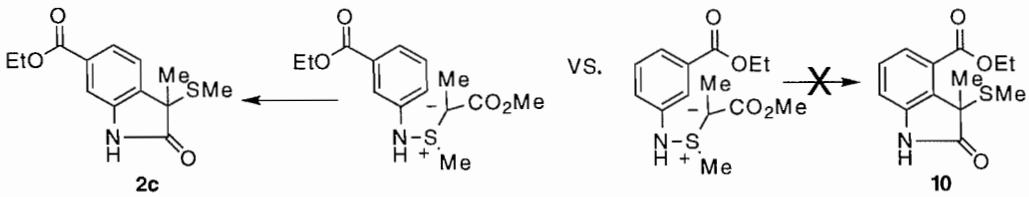
Discussion

It is clear from the results discussed that both the position of the ester group and the substitution pattern at C3 play an important role in the results of the reduction. It seems reasonable that the problem of over-reduction observed for **2a** and **2b** may be ascribed to the presumably high acidity of the proton on C3. Although p*K*a data for these compounds are not available, Gassman has commented on the high acidity of the C3 methine proton, and taken advantage of it in his isatin syntheses (19, 20). Taylor has also commented on problems encountered during ester hydroysis of related structures due to the C3 proton (21). In the case of both **2a** and **2b**, initial deprotonation of the C3 proton would lead to an anion adjacent to the oxindole carbonyl. This increased electron density and enolate character militates against reduction of the oxindole carbonyl group, similar to that reported by Marshall et al. for malonic enolates (22). This C3 anion may also increase the electron density of the ester groups *ortho* or *para* to it by delocalization through the benzene ring, as shown by **4** and **5**. The vinylogous enolate **5** is also quite resistant to addition of hydride. However, once one hydride has added, the aldehyde product **6** is more susceptible to further hydride attack. The next hydride addition results in the benzyloxyaluminate **7**, and the C3 anion, which initially made hydride addition slow, now facil-

Scheme 2.



Scheme 3.



itates over-reduction, perhaps via the *ortho*-quinodimethane **8**. The end result is the 4-methyl oxindole, **3a** or **3b**.

To test the proposed mechanism shown in Scheme 2, **10** was an appealing target. This substrate had the ester at the 4 position and an additional methyl group at C3. Attempted monoalkylation of **2** always resulted in a mixture of products that included starting material, N-alkyl and N,C-dialkylated products.[2] An alternative synthesis relied on the Gassman technique. However, when ethyl (3-amino)benzoate was reacted with methyl (2-thiomethyl)propionate under standard Gassman conditions, the isomeric oxindole **2c** was formed. Although both 4- and 6-substituted oxindoles are possible products from *meta*-substituted anilines, only 4-substituted oxindoles were formed up to this point. As suggested in Scheme **3**, the increased steric demand of the branched sulfide-ester may be responsible for this switch in regiochemistry.

The ester groups of **2c** and **10**, which are *ortho* and *para*, respectively, to the C3 position, are electronically quite similar. Results of the reduction of oxindole **2c** also support the proposed mechanism. The additional methyl group at C3 does not allow enolate formation so the electron density of the ester group *para* to C3 is normal. The free NH still protects the oxindole carbonyl group from reduction. With both $LiEt_3BH$ and $LiAlH_4$, reduction of the ester **2c** to benzylic alcohol **3c** proceeded smoothly.

To finish our study on this series, we examined the reduction of oxindole **2d**. This substrate has a proton on C3, but to which the ester is *meta* (**11**). Although not expecting any interference from the C3 anion, we were interested in seeing what effect the nitrogen would have when placed *ortho* to the ester group. Reduction with $LiAlH_4$ in refluxing THF smoothly afforded the benzylic alcohol, which was inert to further reduction by $LiAlH_4$; no evidence was found to support over-reduction of the C7-benzylic alcohol. Reduction also occurred with $LiEt_3BH$ as the reducing agent. From these results, it seems that delocalization of the nitrogen electron density into the benzene (**12**) ring is probably not favored, since it would result in the loss of any resonance energy associated with the amide resonance (**13**).

Conclusion

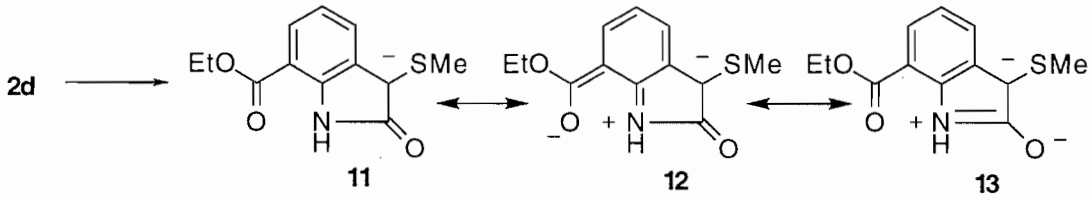
In this paper, we have examined the reduction of a series of 3-(methylthio)oxindoles that had ester groups on the benzene ring. It was found that having a free proton α to the oxindole carbonyl group protects this group from any significant reduction by metal hydrides like $LiEt_3BH$ and $LiAlH_4$. This protection presumably occurs through deprotonation of the amide NH or the methine proton of the oxindole. This resistance to reduction is reminiscent of the situation reported by Marshall, who showed that malonic enolates are not reduced by $LiAlH_4$ (22). Deprotonation of the methine hydrogen also results in donation of significant electron density into the benzene ring. If the ester group is in a position to accept some of this electron density (*ortho* or *para* to C3) then initial reduction is difficult, resulting in the recovery of starting material when mild conditions are used, and in over-reduction of the ester to a methyl group when more vigorous conditions are used.

Experimental

General

All reactions were conducted under an inert atmosphere in flame-dried glassware that had been cooled under a stream of

[2] Reduction of the N-methyl analogue of **10** with $LiAlH_4$ and $LiEt_3BH$ leads to four different products. See accompanying paper.



dry nitrogen. Melting points were determined on a Fisher–Johns Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded with a Bomem MB 101 FT-IR spectrometer with solution cells using the highest grade of methylene chloride available unless otherwise stated. Proton and carbon nuclear magnetic resonance were recorded on either a Bruker AMX-500, Varian XL-300, or Varian Gemini 200 operating at frequencies of 500, 300, and 200 MHz for proton and 125, 75, and 50 MHz for carbon, using the specified solvent, and are reported relative to TMS = 0.00 ppm. Low- and high-resolution mass spectra were recorded on a VG 7070 mass spectrometer or a Concept II instrument. Peak intensities are reported as a percentage of the base peak.

The phrase "usual work-up" refers to drying the solvent over anhydrous magnesium sulfate, filtering, and removing the solvent under reduced pressure using a Buchi Rotovapor. The term chromatography refers to flash chromatography performed using 230–400 mesh silica gel supplied by Terochem Laboratories in the solvent specified. All solvents were routinely distilled prior to use. All starting materials were used as received from commercial sources except for the following: triethylamine was distilled from CaH_2 and THF was dried and distilled from sodium with benzophenone as an indicator; methylene chloride was distilled from P_2O_5 prior to use. *tert*-Butyl hypochlorite was prepared according to the literature immediately before use (23). All manipulations involving *t*-BuOCl, including the preparation, were conducted in the dark. The synthesis of all oxindole starting materials was conducted following the general procedure of Gassman or the modified Gassman approach of Wierenga (16–18). No attempt was made to optimize the syntheses of starting oxindoles.

3-(Methylthio)-4-(carboethoxy)oxindole 2a

Oxindole **2a** was prepared according to the general procedure of Gassman (17). A solution of freshly prepared *t*BuOCl (3.30 g, 30.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a cooled (−78°C) solution of ethyl 3-aminobenzoate (5.00 g, 30.3 mmol) in CH_2Cl_2 (100 mL). The resulting bright yellow mixture was stirred at this temperature for 10 min, at which point a solution of methyl (methylthio)acetate (3.65 g, 30.4 mmol) in CH_2Cl_2 (15 mL) was added and stirring continued for 2.5 h. A solution of triethylamine (3.10 g, 30.7 mmol) in CH_2Cl_2 (15 mL) was then added, and the initially yellow solution was allowed to warm to room temperature (RT) over 12 h. The reddish solution that resulted was poured into a solution of H_2O (200 mL); the organic phase separated and was worked up in the usual manner to provide an orange solid. Recrystallization from CH_2Cl_2–hexanes afforded the title compound as colorless plates (5.70 g, 75%); mp 150–151°C; IR (CH_2Cl_2): 1613, 1723, 3424 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.40 (t, 3H, J = 8.0 Hz), 2.51 (s, 3H), 4.38 (q, 2H, J = 8.0 Hz), 4.68 (s, 1H), 7.02 (d, 1H, J = 8.0 Hz), 7.31 (t, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 8.0 Hz), 8.05 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.15, 14.05, 46.74, 61.33, 113.39, 124.26, 127.89, 128.19, 129.00, 142.04, 165.52, 177.46; EI-MS *m/z* (%): 251 (2.2, M^+), 205 (100), 176 (13.2), 160 (36.6); HRMS calcd. for $C_{12}H_{13}NO_3S$: 251.06162; found: 251.06118.

Reduction of oxindole 2a with $LiAlH_4$: 3-(methylthio)-4-methyloxindole 3a

A solution of oxindole **2a** (100 mg, 0.40 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in THF (10 mL). The resulting gray, cloudy solution was refluxed for 18 h, poured into a saturated solution of potassium sodium tartrate (50 mL) and EtOAc (50 mL), and stirred for 4 h. The organic phase was separated and subjected to normal work-up followed by column chromatography (2:1 hex:EtOAc), providing two compounds: recovered starting material (35 mg, 35%) and a less polar compound, **3a**, isolated as an off-white solid (30 mg, 43%); mp 154–155°C; IR (CH_2Cl_2): 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 2.50 (s, 3H), 4.25 (s, 1H), 6.70 (d, 1H, J = 8.0 Hz), 6.80 (d, 1H, J = 8.0 Hz), 7.20 (t, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.45, 17.85, 45.52, 107.17, 123.27, 124.31, 128.69, 135.96, 140.98, 177.17; EI-MS *m/z* (%): 193 (26.5, M^+), 146 (100), 118 (4.2); HRMS calcd. for $C_{10}H_{11}NOS$: 193.05614; found: 193.05684.

Ethyl 3-(methylamino)benzoate

Adapted from the procedure of Krishnamurthy (24). A round-bottom flask containing a toluene (50 mL) solution of ethyl (3-amino)benzoate (5 g, 30.30 mmol) and formic acid (5 mL, 98%) was equipped with a Dean–Stark trap and heated to reflux for 12 h. The solvent was removed and the resulting purple residue was suspended in CH_2Cl_2 (50 mL), and washed sequentially with H_2O (2 × 20 mL), HCl (10%, 2 × 20 mL), and $NaHCO_3$ (5%, 2 × 20 mL). The organic phase was worked up in the usual manner, affording a dark solid that was triturated with Et_2O, and filtered. The purplish solid was recrystallized from CH_2Cl_2–hexanes and filtered, affording 3.12 g of ethyl 3-(formyl amino)benzoate (53%) as white cubes.

The resulting N-formyl derivative (3.0 g, 15.54 mmol) was dissolved in THF (50 mL), and heated to reflux, at which point a solution of borane – methyl sulfide complex was added (3.0 mL, 10 M, 30.00 mmol) dropwise via syringe. After 12 h at reflux, the solution was cooled to RT, and MeOH (20 mL) was added slowly (**Caution**: H_2 evolution!). Stirring was continued until hydrogen evolution stopped, and then for 15 min longer, after which time the solution was concentrated to dryness, and the residue purified by column chromatography (2:1 hex:EtOAc), affording the title compound as a clear oil (2.5 g, 90%); IR (CH_2Cl_2): 3435, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J = 6.8 Hz), 2.82 (s, 3H), 3.80 (br, 1H), 4.32 (q, 2H, J = 6.8 Hz), 6.74 (d, 1H, J = 6.5 Hz), 7.20 (t, 1H,

J = 6.5 Hz), 7.25 (d, 1H, J = 6.5 Hz), 7.35 (d, 1H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.32, 30.62, 60.79, 112.84, 116.77, 118.23, 129.04, 131.35, 149.34, 167.13; EI-MS *m/z* (%): 179 (100, M^+), 150 (76.0), 134 (40.3), 106 (58.5), 77 (23.2); HRMS calcd. for $C_{10}H_{13}NO_2$: 179.09463; found: 179.09484.

1-Methyl-3-methylthio-4-(carboethoxy)oxindole 2b

Prepared from ethyl (3-*N*-methylamino)benzoate (0.98 g, 5.47 mmol) using the standard Gassman methodology. The orange solid obtained after usual work-up was recrystallized from CH_2Cl_2–hexanes and afforded the title compound as a white solid (175 mg, 12%); mp 82–83°C; IR (CH_2Cl_2): 1717 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40 (t, 3H, J = 7.1 Hz), 1.97 (s, 3H), 3.22 (s, 3H), 4.36 (m, 2H), 4.66 (s, 1H), 6.96 (d, 1H, J = 7.1 Hz), 7.41 (t, 1H, J = 7.1 Hz), 7.65 (d, 1H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.32, 14.04, 26.33, 46.01, 61.30, 111.40, 124.02, 127.33, 127.86, 128.99, 144.72, 165.55, 174.86; EI-MS *m/z* (%): 265 (5.2, M^+), 219 (100), 190 (18.6), 174 (33.8); HRMS calcd. for $C_{13}H_{15}NO_3S$: 265.07727; found: 265.08194.

Reduction of oxindole 2b with $LiAlH_4$; 1-methyl-3-methylthio-4-methyl oxindole 3b

The general procedure outlined above from **2a** was followed. Oxindole **2b** (40 mg, 0.15 mmol) provided, after usual work-up and column chromatography (1:1 hex:EtOAc), compound **3b** as off-white needles (28 mg, 90%); mp 100–101°C; IR (CH_2Cl_2): 1712 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.01 (s, 3H), 2.43 (s, 3H), 3.21 (s, 3H), 4.18 (s, 1H), 6.66 (d, 1H, J = 7.5 Hz), 6.88 (d, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.66, 17.78, 26.01, 44.79, 105.27, 122.54, 124.31, 128.58, 135.53, 143.77, 174.81; EI-MS *m/z* (%): 207 (14.2, M^+), 160 (100), 130 (9.4), 117 (10.4), 77 (7.9); HRMS calcd. for $C_{11}H_{13}NOS$: 207.07179; found: 207.07322.

3-Methyl-3-methylthio-6-(carboethoxy)oxindole 2c

Standard Gassman methodology as reported for the synthesis of **2a** using ethyl (3-amino)benzoate and methyl (2-thiomethyl)propionate afforded, after purification via column chromatography (4:1 hex:EtOAc) and recrystallization from CH_2Cl_2–hexanes, the title compound **2c** as a white solid (24%); mp 135–136°C; IR (CH_2Cl_2): 3421, 1722, 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 7.2 Hz), 1.59 (s, 3H), 1.80 (s, 3H), 4.28 (q, 2H, J = 7.2 Hz), 7.29 (d, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 1.4 Hz), 7.73 (dd, 1H, J = 7.9, 1.4 Hz), 8.38 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.82, 14.01, 21.16, 50.19, 60.98, 110.29, 123.53, 124.53, 130.91, 136.38, 139.61, 165.63, 178.90; EI-MS *m/z* (%): 265 (2.9, M^+), 218 (100), 190 (34.5); HRMS calcd. for $C_{13}H_{15}NO_3S$: 265.07727; found: 265.07661.

Reduction of oxindole 2c with $LiEt_3BH$: 3-methyl-3-methylthio-6-(hydroxymethyl)oxindole 3c

A solution of $LiEt_3BH$ (0.45 mL, 1.0 M in THF, 0.45 mmol) was added dropwise to a cooled (0°C) solution of oxindole **2c** (45 mg, 0.17 mmol) in THF (5 mL). Stirring was continued at 0°C for 1 h, after which time the pale yellow solution was poured into a solution of H_2O (10 mL) and made acidic by the dropwise addition of HCl (10%). Extraction with EtOAc (4 × 20 mL), followed by normal work-up and chromatography (2:3 hex:EtOAc) afforded, in addition to returned starting material (7.8 mg), the title compound **3c**, which was recrystallized from CH_2Cl_2–hexanes as white prisms (27.4 mg, 88%); mp 167–168°C; IR (CH_2Cl_2): 3604, 1729 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 1.80 (s, 3H), 4.60 (s, 2H), 6.85 (s, 1H), 6.95 (d, 1H, J = 7.5 Hz), 7.19 (d, 1H, J = 7.5 Hz), 8.10 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.79, 21.29, 49.98, 64.77, 108.11, 121.13, 123.71, 130.72, 139.78, 141.78, 179.22; EI-MS *m/z* (%): 223 (6.7, M^+), 176 (100), 148 (2.8); HRMS calcd. for $C_{11}H_{13}NO_2S$: 223.06670; found: 223.06858.

3-Methylthio-7-(carboethoxy)oxindole 2d

The modified Gassman conditions of Wierenga et al. were followed (18). A solution of sulfuryl chloride (2.26 g, 16.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cooled solution (−78°C) of methyl (methylthio)acetate (1.83 g, 15.3 mmol) in CH_2Cl_2 (50 mL), resulting in the slow formation of a white precipitate. After stirring for 1 h, a solution of ethyl (2-amino)benzoate (2.50 g, 15.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise, resulting in slow dissolution of the white precipitate with the solution slowly turning pale yellow. After stirring for 2 h, triethylamine (1.59 g, 15.8 mmol) was added, and the solution was allowed to warm to RT overnight. Water (50 mL) was added, and the aqueous layer was separated and subjected to normal work-up conditions, resulting in a yellow semi-solid, which was dissolved in Et_2O (50 mL) and HCl (10%, 10 mL). The two-phase mixture was refluxed for 12 h, cooled, and the organic phase was separated and worked up in the usual manner. Column chromatography (5:1 hex:EtOAc) afforded a yellow solid, which was recrystallized from CH_2Cl_2–hexanes, affording the title compound **2d** as white flakes (383.8 mg, 10.1%); mp 87–88°C; IR (CH_2Cl_2): 3403, 1721, 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, 3H, J = 7.0 Hz), 2.02 (s, 3H), 4.23 (s, 1H), 4.38 (q, 2H, J = 7.0 Hz), 7.08 (t, 1H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.81 (d, 1H, J = 7.5 Hz), 9.20 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.23, 14.32, 45.32, 61.39, 111.73, 122.14, 127.57, 129.58, 129.66, 143.79, 165.85, 175.92; EI-MS *m/z* (%): 251 (3.4, M^+), 205 (100), 158 (40.9), 130 (14.1); HRMS calcd. for $C_{12}H_{13}NO_3S$: 251.06162; found: 251.06239.

Reduction of oxindole 2d with $LiAlH_4$: 3-methylthio-7-(hydroxymethyl) oxindole 3d

Following the procedure described for **3a**, oxindole **2d** (50 mg, 19.9 mg) afforded, after usual work-up and column chromatography (1:1 hex:EtOAc), **3d** as a white crystalline solid (35 mg, 84%); mp 148–149°C; IR (CH_2Cl_2): 3620, 1721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.00 (s, 3H), 4.30 (s, 1H), 4.80 (s, 2H), 7.02 (m, 2H), 7.28 (d, 1H, J = 7.5 Hz), 8.50 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.33, 45.79, 63.43, 120.20, 122.56, 124.54, 127.24, 138.76, 142.36, 168.20; EI-MS *m/z* (%): 209 (7.6, M^+), 163 (100), 144 (42.0), 116 (48.6); HRMS calcd. for $C_{10}H_{11}NO_2S$: 209.05105; found: 209.04985.

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References

1. G.M. Karp. Org. Prep. Proced. Int. **25**, 481 (1993).
2. P.L. Julian and H.C. Printy. J. Am. Chem. Soc. **71**, 3206 (1949).

3. C.B. Hudson and A.V. Robertson. Aust. J. Chem. **20**, 1699 (1967).
4. C.S. Franklin and A.C. White. J. Chem. Soc. 1335 (1963).
5. J.C. Seaton and L. Marion. Can. J. Chem. **35**, 1102 (1957).
6. J.C. Seaton, R. Tondeur, and L. Marion. Can. J. Chem. **36**, 1031 (1958).
7. M. Kates and L. Marion. Can. J. Chem. **29**, 37 (1951).
8. R. Goutarel, M.M. Janot, V. Prelog, R. Sneeden, and W.I. Taylor. Helv. Chim. Acta, **34**, (1951).
9. T. Nishio, N. Okuda, and C. Kashima. Helv. Chim. Acta, **73**, 1719 (1990).
10. B. Schonenberger and A. Brossi. Helv. Chim. Acta, **69**, 1486 (1986).
11. Q.-S. Yu and A. Brossi. Heterocycles, **27**, 1709 (1988).
12. Q.-S. Yu, W.M. Luo, Y.Q. Li, and A. Brossi. Heterocycles, **36**, 1279 (1993).
13. M.E. Pierce, G.F. Huhn, J.H. Jensen, K.W. Sigvardson, Q. Islam, and Y. Xing. J. Heterocycl. Chem. **31**, 17 (1994).
14. F.J. McEvoy and G.R. Allen, Jr. J. Org. Chem. **38**, 3350 (1973).
15. H. Shirowej, S.A. Khan, and H. Plieninger. Synthesis, 84 (1972).
16. P.G. Gassman and T.J. van Bergen. J. Am. Chem. Soc. **95**, 2718 (1973).
17. P.G. Gassman and T.J. van Bergen. J. Am. Chem. Soc. **96**, 5508 (1974).
18. W. Wierenga, J. Griffin, and M.A. Warpehoski. Tetrahedron Lett. **24**, 2437 (1983).
19. P.G. Gassman, B.W. Cue, Jr. and T.-Y. Luh. J. Org. Chem. **42**, 1944 (1977).
20. P.G. Gassman and K.M. Halweg. J. Org. Chem. **44**, 628 (1979).
21. A. Taylor. J. Chem. Res. Synop. 347 (1980).
22. J.A. Marshall, N.H. Andersen, and A.R. Hochstetler. J. Org. Chem. **32**, 113 (1967).
23. M.J. Mintz and C. Walling. Org. Synth. Collect. Vol. **V**, 184 (1973).
24. S. Krishnamurthy. Tetrahedron Lett. **23**, 3315 (1982).