A Strategy to Avoid Anomalous *O*-Alkylation of 4-Hydroxyindole by Diethyl Bromomalonate

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Alkylation of 4-hydroxyindole with diethyl bromomalonate under standard conditions (potassium carbonate–acetone) gave the expected indolyloxymalonate ester **3** together with the anomalous indolyloxy-2-bromomalonate **4**. Depending on conditions, the ratio of the two products varied between 4:1 and 1:2. Protection of the indole nitrogen by a carbobenzyloxy group eliminated formation of the anomalous product.

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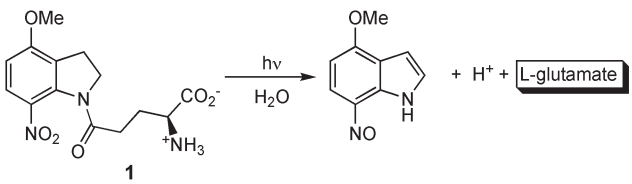
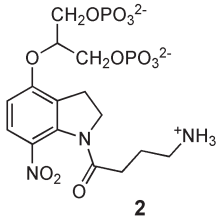
Over the past several years we, and others have developed and applied the photochemistry of 1-acyl-7-nitroindolines as a means to enable rapid (sub-millisecond) application of the neuroactive amino acid L-glutamate onto living neuronal cells [1,2]. At present, the 4-methoxy compound **1** is becoming widely used for this purpose, and an outline of its photochemical cleavage in aqueous solution is shown in Scheme 1. Although the glutamate conjugate **1** is pharmacologically inactive, *i.e.* it has no measurable binding to glutamate receptors prior to photocleavage, similar conjugates with other neuroactive amino acids such as GABA and glycine have been shown to bind to their respective receptors and therefore to blunt the electrophysiological response to photoreleased GABA or glycine respectively [2b]. We have therefore been interested to modify the methoxy group to incorporate a center with high negative charge such as in **2**, in the hope of developing a GABA precursor with such binding reduced or eliminated. As an early intermediate in this projected synthesis, we required the indolyloxymalonate **3**. Several aryloxymalonates are known and have normally been prepared by alkylation of the appropriate phenol with a halomalonate ester [3,4]. Formation of diaryloxymalonates has also been observed as a significant by-product in such reactions, along with products formed by dimerization of the halomalonate [3,4]. Application of this reaction with 4-hydroxyindole gave further unexpected complexities and we describe these results here, together with a means to synthesize **3** without unwanted side reactions.

Scheme 1

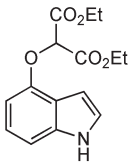


Overall photocleavage reaction of **1**, showing release of L-glutamate.

In the previous work noted above, both chloro- and bromomalonates have been used as alkylating agents. We chose

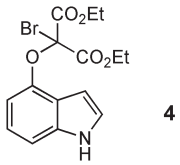


2



3

to use diethyl bromomalonate as it is significantly less expensive than the chloro ester. An initial trial reaction used *p*-cresol as a model phenol, and treatment with diethyl bromomalonate and potassium carbonate in acetone under reflux gave the known [5] diethyl 4-methylphenoxymalonate in excellent yield. However, when the same procedure was applied to 4-hydroxyindole, either as above or with various modifications of temperature and order of addition of reagents, two main aromatic products in varying ratio were always obtained. Tetraethyl 1,1,2,2-ethanetetracarboxylate [3] was also isolated in low yield from a complex mixture when the reaction was performed in refluxing butanone, but was not found in reactions conducted at room temperature in acetone. The two aromatic products were readily characterized as the required malonate **3** and its brominated analogue **4**. The ratio of **3** to **4** (isolated yields) varied between 4:1 and 1:2, with formation of **4** apparently being favored by the use of an excess of the alkylating agent. Trial modifications, such as using Hunig's base in acetonitrile or sodium bicarbonate in DMF, only gave dark reaction mixtures from which no recognizable product could be obtained.



4

So far as we can determine, only two previous examples of compounds analogous to **4** have been described. The corresponding phenoxy compound was formed in low yield by reaction of sodium phenoxide with diethyl dibromoma-

lonate in ethanol [3] while an aryloxychloromalonate was recently reported [6] as ~6% of the total product formed, along with the expected aryloxymalonate, when a tyrosine derivative was treated with diethyl chloromalonate and potassium carbonate in acetone, conditions that are similar to those used in our work above. The mode of formation of the chloromalonate by-product was not further explored in the previous report, although it was noted that the chloro substituent could be removed by hydrogenolysis [6].

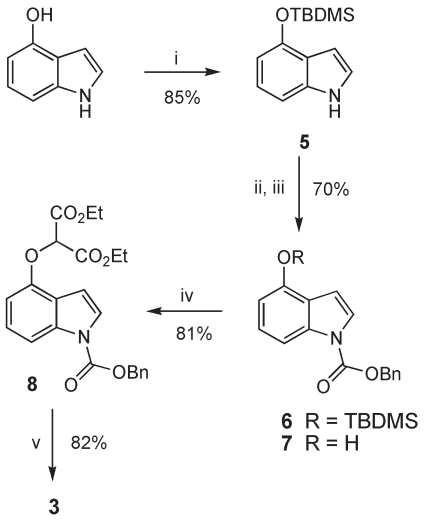
The commercial diethyl bromomalonate that we used contained ~8% of the dibromo ester and we initially considered whether the observed formation of **4** was attributable to the presence of this impurity. Fractional distillation gave a pure sample of the monobromo ester but the use of this purified material did not reduce the yield of **4** compared to that obtained when the unfractionated commercial material was used. We have not tried to determine the mechanistic details of the formation of **4** apart from performing two control experiments. Use of the pure diethyl dibromomalonate under the same alkylation conditions (*i.e.* potassium carbonate in acetone under reflux) gave only a very dark mixture in which the bromoester **4** could not be recognized. Thus the formation of **4** seems not to involve a simple nucleophilic displacement on diethyl dibromomalonate and the very dark color of these reaction mixtures suggests that redox processes involving the hydroxyindole are probably involved. A trial alkylation with diethyl chloromalonate gave a poor recovery of a crude product in which the expected ester **3** was present in low yield, together with more polar material.

Our principal interest was to achieve an effective synthesis of **3** and the most obvious strategy was to decrease the electron density of the hydroxyindole in order to suppress the putative redox chemistry. We considered that the easiest means to achieve such deactivation of the indole was by acylation of its nitrogen atom. The benzyloxycarbonyl (Cbz) group offers both stability under the alkylation conditions and capacity for later removal without perturbing the oxymalonate group. Introduction of this substituent required initial protection of the phenolic group as its TDBMS ether **5**, which was readily achieved with TBDMS chloride–imidazole (Scheme 2). Subsequent acylation of **5** with Cbz chloride followed a method previously applied to indole itself [7], and gave the Cbz derivative **6** in quantitative yield. In this reaction, an excess of ethylenediamine was added when the acylation was complete in order to remove excess Cbz chloride. All by-products could then be removed by simple, non-chromatographic workup to give material suitable for use in the next step without further purification. Removal of the silyl ether with TBAF, buffered with acetic acid to avoid possible hydrolytic cleavage of the Cbz group, cleanly gave the protected hydroxyindole **7**. This compound has previously been prepared in modest yield by photolysis of benzyl 2-oxido-5-isoquinolinylcarbamate, followed by acid treatment of the photolyzate and chromatographic separation of products [8]. This latter route would not easily be suitable for large-scale preparation.

Alkylation of **7** with diethyl bromomalonate gave **8** in 81% yield with no evidence of the brominated by-product, and hydrogenolysis of the Cbz group proceeded cleanly to give material identical with the sample of **3** previously obtained. The overall yield from 4-hydroxyindole was 40% and the procedure was easily carried out on a relatively large scale.

These results confirm that *N*-acylation of 4-hydroxyindole was successful in avoiding the unwanted formation of the bromomalonate derivative **4**. The precise mechanism by which this is achieved remains unclear but it is evident that the particular combination of 4-hydroxyindole and diethyl bromomalonate is necessary to produce the anomalous by-product **4**. In subsequent work, we have found that simple monobromoacetates readily yield the expected indolyloxyacetates upon treatment with unprotected 4-hydroxyindole. Current work is directed to further elaboration of the diester **3** to obtain the GABA conjugate **2**. These results and the pharmacological evaluation of **2** will be reported in due course.

Scheme 2



Reagents and conditions: (i) TBDMS-Cl, imidazole, CH_2Cl_2; (ii) Cbz-Cl, Bu_4NBr, powdered NaOH, CH_2Cl_2; (iii) TBAF, HOAc, THF; (iv) diethyl bromomalonate, K_2CO_3, (v) acetone; H_2, Pd-C, EtOH.

EXPERIMENTAL

^1H nmr spectra were determined on JEOL FX90Q or Varian Unityplus 500 spectrometers in $CDCl_3$ solution with tetramethylsilane as internal reference. Elemental analyses were carried out by MEDAC Ltd., Surrey, U.K. Merck 9385 silica gel was used for flash chromatography. Organic solvents were dried over

anhydrous sodium sulfate and evaporated under reduced pressure. Hexane solvent (bp 40-60°) was redistilled before use.

Reactions of 4-Hydroxyindole with Diethyl Bromomalonate.

(i) A solution of 4-hydroxyindole (266 mg, 2 mmol) in acetone (20 mL) was cooled to 0° under nitrogen and anhydrous potassium carbonate (414 mg, 3 mmol) was added. A solution of commercial diethyl bromomalonate (92%; 624 mg, 2.4 mmol) in acetone (20 mL) was added dropwise over 1 h and the mixture was stirred at 0-5° for 1 h, then at room temperature for further 5 h. The very dark solution was filtered, the solid was washed with acetone and the combined filtrates were evaporated. The residue was dissolved in diethyl ether (50 mL), washed with 0.5 *M* aq. sodium hydroxide and brine, dried and evaporated to a brown viscous oil (535 mg). Flash chromatography (dichloromethane) gave two products. The less polar material was diethyl 2-bromo-2-(indol-4-yloxy)malonate **4** as white crystals (92 mg, 11%), mp 92-93° (from diethyl ether–hexanes); ^{1}H nmr (500 MHz): δ 8.24 (br s, 1H, NH), 7.19 (d, J = 8.1 Hz, 1H, H-7), 7.17 (t, J = 2.7 Hz, 1H, H-2), 7.07 (t, J = 8.1 Hz, 1H, H-6), 6.94 (d, J = 8.1 Hz, 1H, H-5), 6.73-6.75 (m, 1H, H-3), 4.28-4.38 (m, 4H, OCH_2), 1.23 (t, J = 7.1 Hz, 6H, CH_3).

Anal. Calcd. for $C_{15}H_{16}BrNO_5$: C, 48.76; H, 4.36; N, 3.79. Found: C, 48.79; H, 4.43; N, 3.61.

The more polar compound was diethyl 2-(indol-4-yloxy)malonate **3** as white crystals (260 mg, 45%), mp 52-53° (from diethyl ether–hexanes); ^{1}H nmr (500 MHz): δ 8.25 (br s, 1H, NH), 7.13 (dd, J = 3.1, 2.6 Hz, 1H, H-2), 7.09 (d, J = 7.8 Hz, 1H, H-7), 7.05 (t, J = 7.8 Hz, 1H, H-6), 6.76-6.77 (m, 1H, H-3), 6.50 (d, J = 7.5 Hz, 1H, H-5), 5.35 (s, 1H, ArOC*H*), 4.28-4.37 (m, 4H, OCH_2), 1.30 (t, J = 7.1 Hz, 6H, CH_3).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.91; H, 6.17; N, 4.68.

(ii) A solution of 4-hydroxyindole (266 mg, 2 mmol) in acetone (20 mL) was cooled to 0° under nitrogen and anhydrous potassium carbonate (414 mg, 3 mmol) was added. A solution of commercial diethyl bromomalonate (92%; 520 mg, 2 mmol) in acetone (20 mL) was added dropwise. After stirring for 5 h at room temperature, more diethyl bromomalonate (92%; 520 mg) was added and the mixture was stirred at room temperature overnight. Work up and flash chromatography as above afforded **4** (360 mg, 45%) and **3** (123 mg, 21%).

(iii) A solution of 4-hydroxyindole (266 mg, 2 mmol) in acetone (20 mL) was cooled to 0° under nitrogen and anhydrous potassium carbonate (414 mg, 3 mmol) was added. A solution of freshly distilled pure diethyl bromomalonate (574 mg, 2.4 mmol) in acetone (20 mL) was added dropwise and the mixture was stirred at room temperature overnight. Work up and flash chromatography as above afforded **4** (101 mg, 13%) and 3 (199 mg, 34%).

4-(*tert*-Butyldimethylsilyloxy)indole (**5**).

A solution of 4-hydroxyindole (13.31 g, 75 mmol) in dry dichloromethane (400 mL) was treated with imidazole (8.17 g, 120 mmol) and *tert*-butyldimethylsilyl chloride (18.09 g, 120 mmol) and the mixture was stirred at room temperature under nitrogen overnight. The precipitated white solid was filtered off and washed with dichloromethane and the combined filtrates were washed successively with 0.5 *M* aq. hydrochloric acid, 0.5 *M* aq. sodium hydroxide and brine, dried and evaporated to give **5** as white crystals (21.03 g, 85%), mp 80-81° (from hexanes); ^{1}H nmr (500 MHz): δ 8.06 (br s, 1H, NH), 7.08 (dd, J = 3.1, 2.4 Hz, 1H, H-2), 6.99-7.05 (m, 2H, Ar-H), 6.58-6.59 (m, 1H, H-3), 6.52 (dd, J = 7, 1.5 Hz, 1H, H-5), 1.06 (s, 9H, $C(CH_3)_3$), 0.23 (s, 6H, $Si(CH_3)_2$).

Anal. Calcd. for $C_{14}H_{21}NOSi$: C, 67.97; H, 8.56; N, 5.66. Found: C, 67.60; H, 8.80; N, 5.57.

Benzyl 4-(*tert*-Butyldimethylsilyloxy)indole-1-carboxylate (**6**).

A stirred, ice-cold mixture of **5** (18.56 g, 75 mmol), tetrabutylammonium bromide (2.42 g, 7.5 mmol) and powdered sodium hydroxide (4.0 g, 75 mmol) in dichloromethane (375 mL) was treated dropwise with benzyl chloroformate (95% purity; 20.20 g, 112.5 mmol). The reaction mixture was stirred at room temperature and the progress of the reaction was followed by TLC [ethyl acetate–hexanes (1:9)]. Further aliquots of benzyl chloroformate (each 20.20 g) were added after 1 h and 2 h, and the mixture was stirred at room temperature for a total of 18 h, diluted with water and extracted with dichloromethane. The combined organic phases were washed with brine, dried and evaporated. The residual oil was dissolved in dry diethyl ether (250 mL), cooled in ice and treated dropwise with a solution of ethylenediamine (47 mL, 355 mmol) in dry diethyl ether (150 mL) and stirred at room temperature for 0.5 h. The mixture was washed with 0.5 *M* aq. hydrochloric acid and brine and the organic phase was dried and evaporated. After trituration with diethyl ether and cooling in ice, some precipitated *N,N*-di-(benzyloxycarbonyl)ethylenediamine was removed by filtration and **6** was isolated as a pale oil (28.62 g, 100%) which was used in the next step without further purification; ^{1}H nmr (90 MHz): δ 7.78 (d, J = 7.2 Hz, 1H, H-7), 7.00-7.56 (m, 7H, Ar-H), 6.58-6.72 (m, 2H, Ar-H), 5.42 (s, 2H, PhCH_2), 1.03 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$).

Benzyl 4-Hydroxyindole-1-carboxylate (**7**).

A solution of **6** (28.62 g, 75 mmol) in tetrahydrofuran (375 mL) containing acetic acid (4.5 g, 75 mmol) was treated at 0° with 1 *M* tetrabutylammonium fluoride (75 mL, 75 mmol) and the mixture was stirred at 0° for 40 min. The solvent was evaporated and the residue was dissolved in diethyl ether (250 mL) and washed with saturated aq. sodium bicarbonate and brine, dried and evaporated to give a brown solid which was washed with cold hexanes to give **7** as white fluffy needles (14.13 g, 70%), mp 118-120° (from dichloromethane–hexanes), (lit. [8] mp 121-124°).

Benzyl 4-[Di(ethoxycarbonyl)methoxy]indole-1-carboxylate (**8**).

The indole **7** (10.69 g, 40 mmol) was added to a suspension of anhydrous potassium carbonate (8.29 g, 60 mmol) in acetone (400 mL) and the mixture was stirred at room temperature for 15 min. Diethyl bromomalonate (11.47 g, 48 mmol) was added and the mixture was heated under reflux for 17 h. The solid was filtered off and washed with acetone and the combined filtrates were evaporated. The residue was dissolved in diethyl ether (150 mL), washed with 0.5 *M* aq. sodium hydroxide and brine, dried and evaporated to give a brown viscous oil (16.87 g). After trituration with diethyl ether, the precipitated white solid was filtered off and the filtrate was evaporated. The residue was flash chromatographed [ethyl acetate–hexanes (15:85)] to give more solid and the combined solids were recrystallized to give **8** as white crystals (13.83 g, 81%), mp 77-78° (from ethyl acetate–hexanes); ^{1}H nmr (500 MHz) δ 7.86-7.92 (br d, 1H, H-7), 7.57 (d, J = 3.7 Hz, 1H, H-2), 7.47-7.49 (m, 2H, Ph-H), 7.36-7.43 (m, 3H, Ph-H), 7.20 (t, J = 8.1 Hz, 1H, H-6), 6.86 (d, J = 3.9 Hz, 1H, H-3), 6.63 (d, J = 8.1 Hz, 1H, H-5), 5.45 (s, 2H, PhCH_2), 5.30 (s, 1H, ArOC*H*), 4.29-4.37 (m, 4H, OCH_2), 1.30 (t, J = 7.1 Hz, 6H, CH_3).

Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.06; H, 5.64; N, 3.21.

Diethyl 2-(Indol-4-yloxy)malonate (**3**).

A solution of **8** (8.51 g, 20 mmol) in ethanol (250 mL) was mixed with 10% palladium on carbon (1.5 g) and hydrogenated at atmospheric pressure for 1 h until hydrogen uptake ceased. The catalyst was filtered off through a Celite bed and washed with ethanol, and the filtrate was evaporated to give a brown oil. Filtration through flash silica with ethyl acetate–hexanes (3:2) as eluent, followed by trituration with diethyl ether–hexanes at -20° gave **3** as white crystals (4.78 g, 82%), mp 52-53° (from diethyl ether–hexanes) identical to the material described above.

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