Syntheses of 2(5)-Substituted 1-Acetyl-3-oxo-2,3-dihydroindoles, 3-Acetoxy-1-acetylindoles, and of 2-Methyl-5-methoxyindole-3-acetic Acid

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2-Methyl-5-methoxyindole-3-acetic acid **(11a)** is a key intermediate in the synthesis of drugs such as indomethacin[1]. We now report that the Wittig-Horner reaction of 1-acetyl-2-methyl-5-methoxy-3-oxoindoline **(6a)** provides an efficient route to **11a**. The usual access to **6a**, however, involves condensa-

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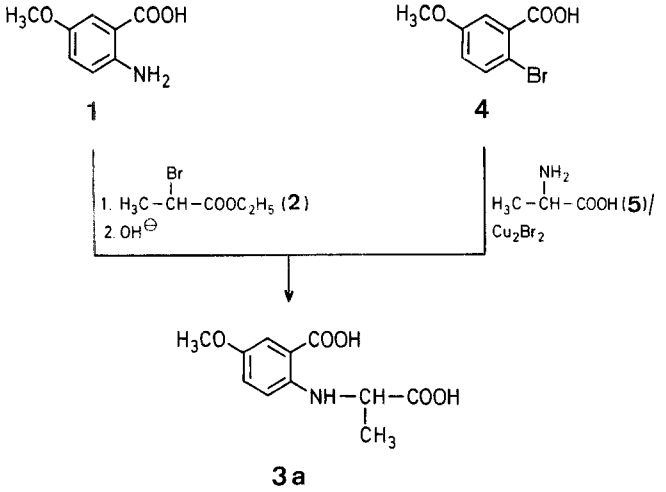
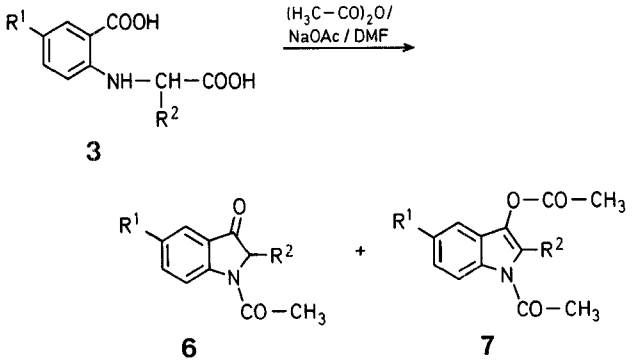
tion of 5-methoxyanthranilic acid (**1**)[2,3,4] with 2-bromopropanoic acid (or its ethyl ester **2**) to give *N*-(2-carboxy-4-methoxyphenyl)-D,L-alanine (**3a**)[5]. We have now found that 2-bromo-5-methoxybenzoic acid (**4**)[6] can be condensed with alanine (**5**) in the presence of copper(I) bromide as catalyst to give **3a**. Use of optically active alanine gives optically active **3a**. Glycine reacts similarly at 100 °C as described for its reaction with 5-benzoyloxy-2-bromobenzoic acid[7].



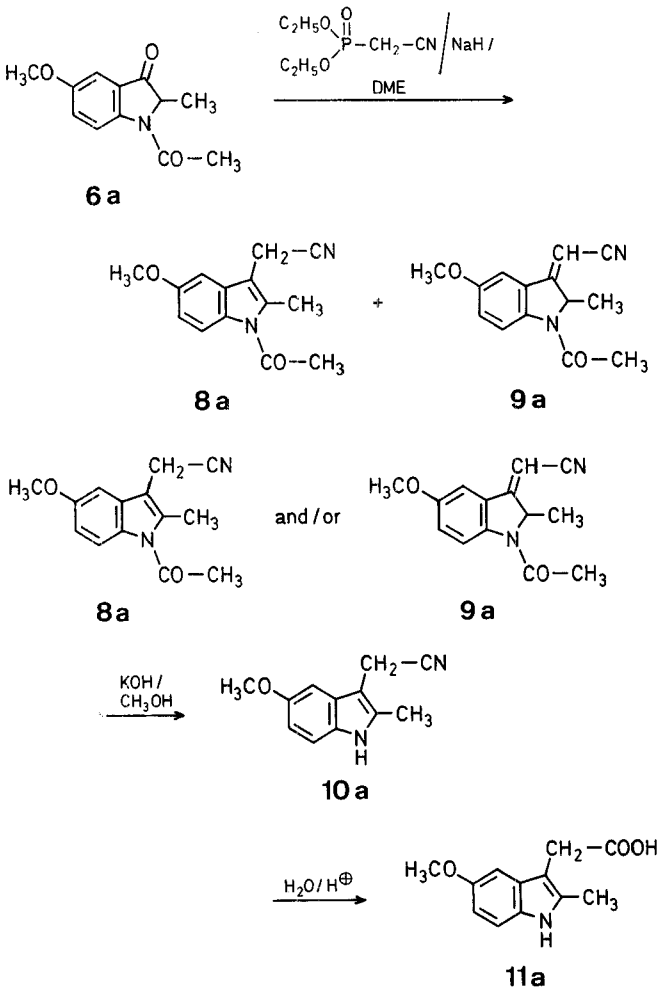
Cyclization of **3a** by heating with acetic anhydride and sodium acetate gave only low yields of the 3-oxoindoline **6a** and its enol acetate **7a**. The methyl group in the 2-position is probably responsible for the low yields, as reported previously for the related product **3b**[8,9]. We have improved the yields of **6a** and **7a** by using dimethylformamide as solvent with 10 equiv of acetic anhydride and 4 equiv of sodium acetate as reagent system. The resultant mixture of the keto (**6a**) and *O*-acetyl (**7a**) forms can be separated if necessary. Product **7a** is selectively deacetylated to **6a** by treatment with aqueous sodium sulfite. The keto product **6a** is directly obtained by this modified procedure in a ratio of **6a** : **7a** = 40 : 60 whereas in the original method it was only formed in traces.



3,6,7	R^1	R^2
a	H_3CO	CH_3
b	H	CH_3
c	H_3C	CH_3
d	H	C_2H_5
e	H	C_6H_5

The yield of the cyclization reaction could not be further improved by prior *N*-acetylation. Cyclization of optically active **3a** gives a mixture of racemic **6a** and **7a**. The properties of compounds **3**, **6**, and **7** prepared are listed in Tables 1, 2, and 3.

Attempts to react **6a** with the sodium salt of diethyl ethoxycarbonylmethanephosphonate[13] or with the lithium salt of ethyl trimethylsilylacetate, known to react with enolizable ketones[11,14], failed. However, the Wittig-Horner reaction of **6a** with the sodium salt of diethyl cyanomethanephosphonate gave a mixture of **8a** and **9a** in 85% yield. The ratio **8a** : **9a** depends on the experimental conditions used (the presence of traces of sodium hydroxide increases this value). Compounds **8a** and **9a** were deacetylated with potassium hydroxide in methanol to the nitrile **10a**, which on acidic hydrolysis yielded the desired acid **11a**.



1-Acetyl-2-methyl-3-oxo-2,3-dihydroindole (**6b**) reacts similarly in the Wittig-Horner reaction to give a mixture of products **8b** and **9b** having *endo*- and *exo*-cyclic double bonds, respectively.

In the ^{1}H-N.M.R. spectra of **9a** and **9b**, only one signal is observed for the olefinic proton ($\delta = 5.50$ ppm, d, $J = 2.5$ Hz) and spin-decoupling studies indicate that this signal is not due to a mixture of (*E*)- and (*Z*)-isomers. A small allylic coupling constant has been reported for the (*Z*)-isomer of 2-alkyl-1-cyano-2-phenylethenes[15].

The *N*-phenylamino acids **3b–e** were prepared according to reported procedures[8,10,12]. 2-Bromo-5-methoxybenzoic acid (**4**) was prepared by a modification of the method of Ref.[6]; yield: 68%, uncontaminated by isomeric bromides and of sufficient purity for further use; m.p. 160 °C.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.75$ (s, 3 H, OCH_3); 7.2 (m, 3 H_{arom}); 7.3 ppm (br. s, 1 H, COOH).

***N*-(2-Carboxy-4-methoxyphenyl)-D,L-alanine (3a):**

To a solution of 4 (120 g, 0.52 mol) in aqueous potassium hydroxide solution (87 g, 1.55 mol in 400 ml water), alanine (**5**; 93 g, 1.04 mol), anhydrous potassium carbonate (147 g, 1.06 mol), and copper(I) bro-

mide (2 g) are added in a reaction pressure vessel. The mixture is heated to 160 °C during 2 h and held at this temperature for 3 h, cooled, and the mixture filtered to remove precipitated copper. The solution is acidified to pH 3 with concentrated hydrochloric acid, extracted with ethyl acetate (3 × 200 ml), the extract is washed with water (4 × 100 ml), dried with magnesium sulfate, and evaporated to give crude **3a** as a solid. This residue is washed with 20:80 acetic acid/water to leave **3a** of sufficient purity for the next step; yield: 73 g (59%); m.p. 175 °C.

(+)-L-Alanine and (−)-D-alanine react similarly to give optically active **3a** in the same yield; (+)-**3a**; m.p. 162 °C; $[\alpha]_D^{20}$: +104 ± 1° (*c* 2, DMF); (−)-**(3a)**; m.p. 162 °C; $[\alpha]_D^{20}$: −104 ± 1° (*c* 2, DMF).

Cyclization of Compounds 3; General Procedure:
Compound **3** (0.05 mol) is dissolved in dimethylformamide (125 ml) containing dry sodium acetate (16 g, 0.2 mol). Acetic anhydride (50 ml, 0.5 mol) is added dropwise under nitrogen and the mixture is then heated under reflux for 2 h. The solvent is evaporated, the residue is poured into water (100 ml), extracted with chloroform (3 × 50 ml), washed with aqueous sodium carbonate solution (3 × 50 ml), and with water (3 × 50 ml). The organic layer is dried with magnesium sulfate, evaporated, and the resultant crude oil is chromatographed on neutral alumina using 4:1 cyclohexane/dichloromethane as eluent. Compound **7** is eluted first, followed by compound **6** (Table). Compounds **7** are easily transformed into **6** by the reported procedure[5,7,10].

Table 1. *N*-(2-Carboxyphenyl)-amino Acids **3** prepared

Product No.	Yield [%]		m.p. [°C]		^{1}H-N.M.R. (CDCl$_3$ or DMSO-d_6/TMS) δ [ppm]
	found	reported	found	reported	
3a	59	—	175°	175°[5]	1.50 (d, 3H, CH_3, J=7 Hz); 3.65 (s, 3H, OCH_3); 4.05 (q, 1H, CH); 6.4–7.2 (m, 3H$_{arom}$); 10.0 (br. s, 3H, OH + NH)
3b	65	68[10]	200°	200°[10]; 210°[12]; 216°[8]	1.50 (d, 3H, CH_3, J=7 Hz); 4.10 (q, 1H, CH, J=7 Hz); 8.10 (br. s, 1H, NH); 12.0 (br. s, 2H, COOH); 6.4–7.9 (m, 4H$_{arom}$)
3c	54	—	225°	—[a]	1.45 (d, 3H, CH_3, J=7 Hz); 2.15 (s, 3H, CH_3); 4.01 (q, 1H, CH); 6.4–7.7 (m, 3H$_{arom}$); 9.6 (br. s, 3H, OH + NH)
3d	72	70[11]	218°	195°[11]; 215°[8]	1.05 (t, 3H, CH_3, J=7 Hz); 2.0 (m, 2H, CH_2); 4.02 (t, 1H, CH, J=6 Hz); 6.5–8.1 (m, 4H$_{arom}$); 8.1 (br. s, 1H, NH or OH); 11.5 (br. s, 2H, OH or NH)
3e	41	44[10]	226°	195°[10]; 203°[12]; 222°[8]	5.15 (s, 1H, CH); 6.3–7.9 (m, 9H$_{arom}$); 8.9 (br. s, 1H, NH or OH); 11.6 (br. s, 2H, OH or NH)

[a] $C_{11}H_{13}NO_4$ (223.2)	calc.	C 59.14	H 5.87	N 6.28
	found	59.01	6.03	6.45

Table 2. 2,5-Substituted 1-Acetyl-3-oxo-2,3-dihydroindoles **6** prepared

Product	Yield [%] of **6**+**7**		m.p. [°C] of **6**		I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
	found	reported	found	reported		
6a	60	25–35[5]	125°	125°[5]	1705, 1650	1.57 (d, 3H, CH_3, J=7 Hz); 2.30 (s, 3H, CO—CH_3); 3.80 (s, 3H, OCH_3); 4.25 (q, 1H, CH, J=7 Hz); 7.0–8.3 (m, 3H$_{arom}$)
6b	65	30[8,10]	104°	85–98°[8,10]	1715, 1660	1.54 (d, 3H, CH_3, J=7 Hz); 2.35 (s, 3H, CO—CH_3); 4.24 (q, 1H, CH, J=7 Hz); 7.3–8.4 (m, 4H$_{arom}$)
6c	50	—	122°	—[a]	1715, 1670	1.57 (d, 3H, CH_3, J=7 Hz); 2.32 (s, 3H, CH_3); 2.36 (s, 3H, CO—CH_3); 4.30 (q, 1H, CH, J=7 Hz); 7.1–8.4 (m, 3H$_{arom}$)
6d	55	—	65°	—[b]	1710, 1675	0.78 (t, 3H, CH_3, J=7 Hz); 2.15 (m, 2H, CH_2); 2.4 (m, 3H, CO—CH_3); 4.4 (m, 1H, CH); 7.1–8.4 (m, 4H$_{arom}$)
6e	72	35[10]	137°	139°[8,10]	1710, 1675	2.07 (s, 3H, CO—CH_3); 5.17 (s, 1H, CH); 7.2–8.6 (m, 9H$_{arom}$)

[a] $C_{12}H_{13}NO_2$ (203.2)	calc.	C 70.91	H 6.45	N 6.89
	found	70.71	6.41	7.10
[b] $C_{12}H_{13}NO_2$ (203.2)	calc.	C 70.91	H 6.45	N 6.89
	found	71.16	6.32	6.83

Table 3. 2,5-Substituted 3-Acetoxy-1-acetylindoles **7** prepared

Product	m.p. [°C] of **7**		I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
	found	reported		
7a	119°	118°[5]	1735, 1690	2.35 (s, 3H, CO—CH_3); 2.40 (s, 3H, CO—CH_3); 3.78 (s, 3H, OCH_3); 6.9–7.9 (m, 3H$_{arom}$)
7b	126°	126°[8]; 134°[8]	1760, 1705	2.30 (s, 3H, CO—CH_3); 2.37 (s, 3H, CH_3); 2.58 (s, 3H, CO—CH_3); 7.1–8.0 (m, 4H$_{arom}$)
7c	70°	—[a]	1765, 1685	2.40 (s, 6H, CO—CH_3); 2.45 (s, 3H, CH_3); 2.65 (s, 3H, CH_3); 7.0–7.9 (m, 3H$_{arom}$)
7d	130°	128°[8]	1755, 1700	1.25 (t, 3H, CH_3); 2.42 (s, 3H, CO—CH_3); 3.0 (m, 2H, CH_2); 2.80 (s, 3H, CO—CH_3); 7.0–7.9 (m, 4H$_{arom}$)
7e	130°	126°[8]	1775, 1765, 1705	1.95 (s, 3H, CO—CH_3); 2.15 (s, 3H, CO—CH_3); 7.2–8.3 (m, 9H$_{arom}$)

[a] $C_{14}H_{15}NO_3$ (245.3)	calc.	C 68.55	H 6.16	N 5.71
	found	68.77	6.02	5.59

1-Acetyl-3-cyanomethyl-5-methoxy-2-methylindole (8a):
Sodium hydride (50% suspension in mineral oil, 0.53 g, 0.011 mol) is washed with ether and suspended in dimethoxyethane (20 ml) under nitrogen and then cooled to 0 °C. A solution of diethyl cyanomethanephosphonate (1.95 g, 0.011 mol) in dimethoxyethane (10 ml) is added dropwise to the stirred mixture at 0 °C. After 10 min, the mixture is diluted with dimethoxyethane (20 ml) and indole **6a** (2.19 g, 0.01 mol) is added portionwise. The mixture is stirred for 3 h at room temperature, poured into acidified ice/water (150 ml, pH 5) whereupon crude **8a** crystallizes. The yellow product is filtered and dried; yield: 1.6 g (66%); m.p. 132 °C.

$C_{14}H_{14}N_2O_2$	calc.	C 69.39	H 5.83	N 11.57
(242.1)	found	69.10	5.84	11.51

I.R. (KBr): $\nu = 2240$ (CN), 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.50$ (s, 3H, CH_3); 2.65 (s, 3H, CO—CH_3); 3.60 (s, 2H, CH_2); 3.80 (s, 3H, OCH_3); 6.7–6.9 (m, 2H_{arom}); 7.65 ppm (m, 1H_{arom}).

The filtrate from above is extracted with dichloromethane (3 × 20 ml), the extract dried with magnesium sulfate, and evaporated to give a mixture of **8a**, **9a**, **10a**, and traces of unreacted **6a** as an oil; yield: 0.65 g.

Column chromatography of this oily residue on silica gel eluting with 3:1 hexane/dichloromethane gives *1-acetyl-5-methoxy-2-methyl-3-cyanomethylene-2,3-dihydroindole* **(9a)**; yield: 0.46 g (19%); m.p. 140 °C. This product is sometimes obtained directly by crystallization of the above reaction mixture after hydrolysis.

$C_{14}H_{14}N_2O_2$	calc.	C 69.39	H 5.85	N 11.57
(242.1)	found	69.55	5.68	11.39

I.R. (KBr): $\nu = 2200$ (CN); 1640 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.65$ (d, 3H, CH_3); 2.35 (s, 3H, CO—CH_3); 3.80 (s, 3H, OCH_3); 5.15 (m, 1H, CH); 5.50 (d, 1H, =CH, $J = 2.5$ Hz); 6.9–7.3 (m, 2H_{arom}); 8.25 ppm (m, 1H_{arom}).

1-Acetyl-3-cyanomethyl-2-methylindole (8b):
Prepared as described for **8a** starting with **6b** (1.89 g, 0.01 mol), except that **8b** does not crystallize from the reaction mixture after addition of water. The resultant oil is extracted with dichloromethane (3 × 20 ml), the extract dried with magnesium sulfate, and evaporated in vacuo to leave a mixture of **8b**, **9b**, **10b**, and unreacted **6b** (< 5%). (Compound **9b** sometimes crystallizes from this residue). The residue is column chromatographed on silica gel using 3:1 petroleum ether (b.p. 40–60 °C)/dichloromethane as eluent to give first 1-acetyl-3-cyanomethyl-2-methylindole **(8b)**, then 1-acetyl-3-cyanomethylene-2-methyl-2,3-dihydroindole **(9b)**, and 2-methyl-3-cyanomethylindole **(10b)**.

8b; yield: 0.78 g (37%); oil.

$C_{13}H_{12}N_2O$	calc.	C 73.55	H 5.70	N 13.20
(212.1)	found	73.29	5.47	13.42

I.R. (film): $\nu = 2240$ (CN); 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.50$ (s, 3H, CO—CH_3); 2.63 (s, 3H, CO—CH_3); 3.56 (s, 2H, CH_2); 7.0–8.1 ppm (m, 4H_{arom}).

9b; yield: 0.65 g (31%); m.p. 122 °C.

$C_{13}H_{12}N_2O$	calc.	C 73.55	H 5.70	N 13.20
(212.1)	found	73.28	5.91	13.15

I.R. (KBr): $\nu = 2200$ (CN); 1665 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.65$ (d, 3H, CH_3, $J = 7$ Hz); 2.40 (s, 3H, CO—CH_3); 5.25 (m, 1H, CH); 5.65 (d, 1H, CH—CN, $J = 2.5$ Hz); 7.1–8.1 ppm (m, 4H_{arom}).

5-Methoxy-2-methyl-3-cyanomethylindole (10a):
The oily mixture of **8a** and **9a** or compound **8a** alone (1.0 g, 4.1 mmol) is dissolved in methanol (25 ml) containing potassium hydroxide (2.8 g, 0.05 mol). The mixture is stirred for 3 h at room temperature and poured into water (100 ml). The precipitated solid **10a** is recrystallized from ethanol; yield: 0.80 g (97%); m.p. 112 °C.

$C_{12}H_{12}N_2O$	calc.	C 71.96	H 6.04	N 14.00
(200.1)	found	72.25	5.81	13.73

I.R. (KBr): $\nu = 3320$ (NH); 2240 cm^{-1} (CN).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3); 3.65 (s, 2H, CH_2); 3.80 (s, 3H, OCH_3); 6.6–7.2 (m, 3H_{arom}); 7.85 ppm (br. s, 1H, NH).

2-Methyl-3-cyanomethylindole (10b):
Prepared as described for **10a** starting from the oily mixture of **8b** and **9b** (2.0 g, 0.01 mol) and recrystallized from ethanol; yield: 1.56 g (92%); m.p. 84 °C.

$C_{11}H_{10}N_2$	calc.	C 77.60	H 5.95	N 16.46
(170.1)	found	77.43	6.09	16.53

I.R. (KBr): $\nu = 3380$ (NH); 2240 cm^{-1} (CN).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.25$ (s, 3H, CH_3); 3.58 (s, 2H, CH_2); 7.1–7.6 (m, 4H_{arom}); 8.05 ppm (br. s, 1H, NH).

5-Methoxy-2-methylindole-3-acetic Acid (11a):
Compound **10a** (1.0 g, 5 mmol) is heated for 6 h with concentrated sulfuric acid (4 ml) and water (14 ml). The mixture is then poured into water (80 ml) and extracted at pH 6 with dichloromethane (3 × 15 ml). The combined extracts are washed with water and dried with magnesium sulfate. Evaporation of the solvent gives the solid product which is recrystallized from ethanol; yield: 0.65 g (59%); m.p. 162 °C (Ref.[1], m.p. 159 °C.

I.R. (KBr): $\nu = 3350$ (NH); 1725 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/DMSO-d_6): $\delta = 2.30$ (s, 3H, CH_3); 3.50 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 6.4–7.1 (m, 4H, H_{arom} + OH or NH); 10.3 ppm (br. s, 1H, OH or NH).

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