214. Synthesis of Esters of 3-(2-Aminoethyl)-1*H*-indole-2-acetic Acid and 3-(2-Aminoethyl)-1*H*-indole-2-malonic Acid (= 2-[3-(2-Aminoethyl)-1*H*-indol-2-yl]propanedioic Acid)

4th Communication on Indoles, Indolenines, and Indolines[1])

by **Siavosh Mahboobi** and **Karl Bernauer***

Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH–8057 Zürich
and Pharmazeutische Forschungsabteilung der *F. Hoffmann-La Roche & Co. AG*, CH–4002 Basel

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Alkyl 3-(2-aminoethyl)-1*H*-indole-2-acetates **6a** and **6b** are synthesized starting from methyl 1*H*-indole-2-acetate (**2**) *via* methyl 3-(2-nitroethenyl)-1*H*-indole-2-acetate (**4**) and the alkyl 3-(2-nitroethyl)-1*H*-indole-2-acetates **5a** and **5b** *(Scheme 1)*. Analogously, diisopropyl 3-(2-aminoethyl)-1*H*-indole-2-malonate **20b** is obtained from diisopropyl 1*H*-indole-2-malonate **11c** *(Scheme 4)*. An alternative synthesis of **20a** and **20b** follows a route *via* **15**–**18** and the dialkyl 3-(2-azidoethyl)-1*H*-indole-2-malonates **19a** and **19b**, respectively *(Scheme 3)*. The aminoethyl compounds **6a** and **20a** are easily transformed into lactams **7** and **21**, respectively. Procedures for the preparation of the indoles **2** and **11a** and of the alkylating agent **14** are described. A tautomer **12** of **11a** is isolated.

1. Introduction. – Compounds of type **6** and **20** are needed by us in programs aiming at syntheses of tricyclic indole derivatives and of indole alkaloids [1b]. In the following, we report on convenient and high-yield procedures for their preparation.

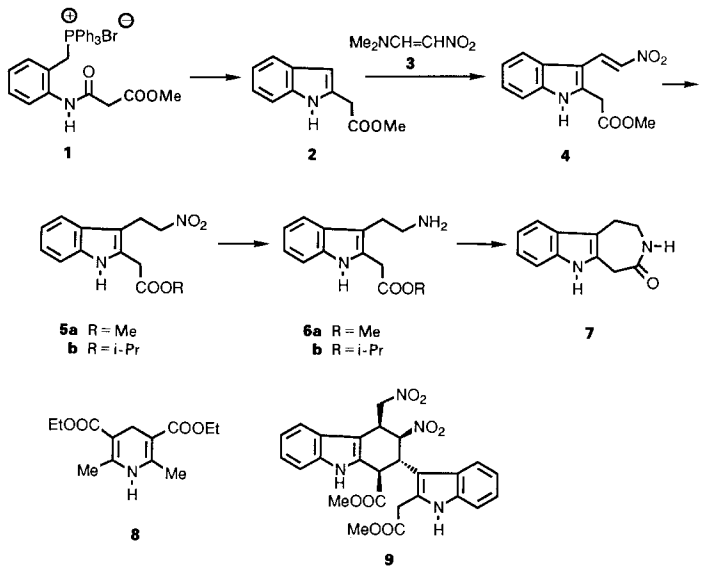
Synthetic routes to **6** and **20** *via* esters **2** and **11** of 1*H*-indole-2-acetic acid and 1*H*-indole-2-malonic acid (= 2-(1*H*-indol-2-yl)propanedioic acid), respectively, were chosen *a priori* since side chains are easily introduced into the 3-position of 2-substituted 1*H*-indoles [2] [3]. The amino esters **6** and **20** were not expected to be very stable. Therefore, the syntheses were designed to pass through stable intermediates, namely 3-(2-nitroethyl) and 3-(2-azidoethyl) derivatives (**5**, **23**, and **19**), respectively, which could serve as stock compounds, easily transformable into the amino esters.

2. Alkyl 3-(2-Aminoethyl)-1*H*-indole-2-acetates 6 *(Scheme 1)*. – For alkyl 1*H*-indole-2-acetates, required as starting compounds, several syntheses are reported [4–6]. We decided to make use of the principle described by *Capuano* and coworkers [6], the essential feature of which is an intramolecular *Wittig*-type reaction (**1**→**2**). With the methyl ester **1** and sodium *tert*-pentylate as base we achieved yields of **2** in the range of 65–70%. The C_2-side chain was introduced into **2** by reaction with *N,N*-dimethyl-2-nitroethenamine (**3**) [7]. The product **4** was not very stable in solution (self-condensation), but precipitated from the reaction mixture in sufficiently pure form (> 85%). The C=C bond of the side chain was reduced by the *Hantzsch* ester **8** in presence of silica gel in refluxing benzene [8], giving **5a** in 60–65% yield besides a dimer **9**[2]) of compound **4**. Later

[1]) 3rd Communication, see [1a].

[2]) We will report on the preparation and structure of **9** and related dimers in a forthcoming paper.

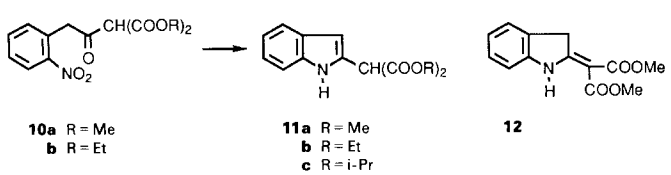
Scheme 1



on, it was found[3]) that hydrogenation with *Wilkinson* catalyst (see *Exper. Part*) is the method of choice for the transformation **4**→**5a** (yield > 90%). The hydrogenation of **5a** at 0° in MeOH over Pd/C was very fast (after a short induction period) and afforded the amine **6a** in quantitative yield. Compound **6a** lactamized easily into **7** [9], particularly in presence of catalytic amounts of acid. The methyl ester **5a** could be transesterified by the orthotitanate method [10] yielding the isopropyl ester **5b** (90%). Its hydrogenation product **6b** was more stable than **6a** and easy to crystallize.

3. Dialkyl 1*H*-Indole-2-malonates 11 *(Scheme 2).* – The 2-nitrobenzyl ketones, on catalytic hydrogenation of the nitro group, spontaneously form the corresponding 1*H*-indoles [11]. This applies also to esters **10** of [(2-nitrophenyl)acetyl]malonic acid. *Rosenmund* and coworkers [12] described the formation (in modest yield) of the diethyl ester **11b** *via* **10b**. We obtained the dimethyl ester **10a** by reaction of (2-nitrophenyl)acetyl chloride with the methoxy-magnesium derivative of dimethyl malonate[4]) (75–80%). Hydrogenation of **10a** over Pd/C afforded dimethyl 1*H*-indole-2-malonate **11a** (80%). Occasionally, the tautomer **12** of **11a** was observed, *e.g.* when **11a** was purified by chromatography.

Scheme 2



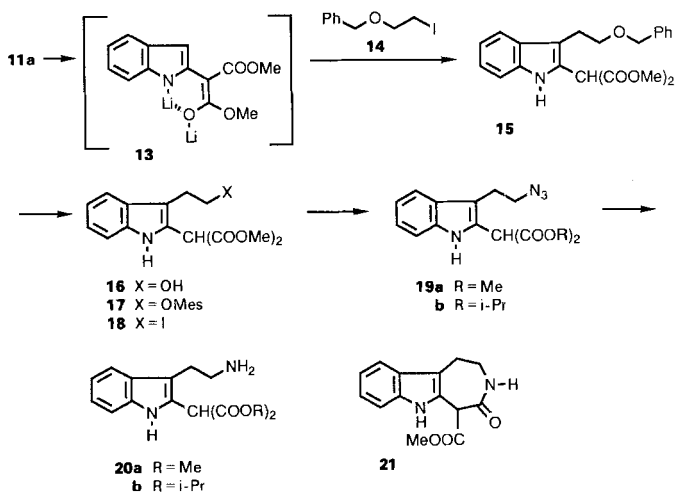
[3]) Hydrogenation studies by Dr. *A. Roessler* and Mr. *E. Fiechter*.

[4]) The preparation of a corresponding derivative of diethyl malonate is described [13].

Compound **11a** was transesterified in presence of tetraisopropyl orthotitanate into the diisopropyl ester **11c** (90%).

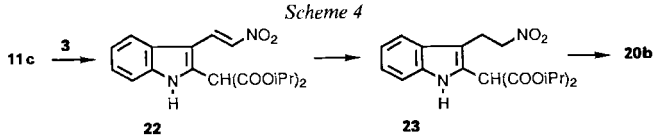
4. Dialkyl 3-(2-Aminoethyl)-1*H*-indole-2-malonates 20 *(Scheme 3)*. – The essential step in this synthesis is the alkylation of dimethyl ester **11a** with 2-(benzyloxy)ethyl iodide (**14**). For **14** [14], we have developed a high-yield synthesis starting from ethylene glycol, suitable for preparation on a large scale. The ester **11a** was metallated in THF with 2 equiv. of the Li salt of hexamethyldisilazane (→**13**) and subsequently reacted with **14** at reflux temperature. The product **15**, after chromatography[5]), was transformed into the crystalline 3-(2-hydroxyethyl)-1*H*-indole-2-malonate **16** (57% from **11a**) by catalytic hydrogenation. The amino ester **20a** was obtained from **16** *via* the mesylate **17** (not purified), the iodide **18** (stable), and the azide **19a** (72% overall). Because of the proneness of **20a** to lactamization (→**21**), azide **19a** was hydrogenated at 0°. Compound **19a** was transesterified by the orthotitanate procedure into the very stable diisopropyl ester **19b** (80–85%). The amino ester **20b**, obtained from **19b**, was more stable than **20a**.

Scheme 3



5. Diisopropyl 3-(2-Aminoethyl)-1*H*-indole-2-malonate 20b *(Scheme 4)*. – In a second, shorter synthetic variant, the diisopropyl ester **11c** was reacted with *N,N*-dimethyl-2-nitroethenamine (**3**), as described in *Chapt. 2* for compound **2**. The product **22** (80–85%) was much more stable than **4**. Selective reduction of the double bond of the side chain by $NaBH_4$ in presence of silica gel [14] yielded the very stable **23** (75–80%). The latter was then hydrogenated (short induction period) in 2-propanol at 40° over Pd/C to give **20b** (88%).

Scheme 4



[5]) Remaining **14** had to be completely removed; it blocked as a catalyst poison the hydrogenation of **15**.

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Experimental Part

General. Reagent-grade solvents *(Fluka, Merck)* were dried over molecular sieves. Pd/C, type *E 101 N/D*, was from *Degussa*. All reactions were performed in closed systems under a slight Ar pressure. Evaporation means removal of solvent by use of a *Büchi* rotary evaporator at 40–60°/*in vacuo* (20–400 Torr) followed by evaporation at 10^{-2} Torr. Crystalline substances, in all cases, were dried *in vacuo* (< 0.1 Torr). Column chromatography: silica gel *60* (0.04–0.063 mm; *Merck*). M.p.: uncorrected; *Büchi 510*. IR spectra: *Nicolet-7199-FT-IR* spectrophotometer and *PE-781;* in cm^{-1}. ^{1}H-NMR spectra: *Varian-EM-390* (90 MHz) and *-XL-200* (200 MHz) spectrometer; *Bruker-Spectrospin-A5-250* (250 MHz), *-WM-400*, and *-AM-400* (400 MHz) spectrometer; δ in ppm rel. to internal TMS, coupling constants J in Hz. MS: *MS9* updated with a *Finnigan ZAB* console, data system *SS200, VG Altrincham* (EI: 70 eV); *Varian MAT 1125; m/z* (% of the base peak).

1. *{2-[2-(Methoxycarbonyl)acetamido]benzyl}triphenylphosphonium Bromide* (**1**). Methyl 3-chloro-3-oxopropanoate (47.8 g, 0.35 mol) was slowly dropped into a stirred mixture of (2-aminobenzyl)triphenylphosphonium bromide [6] (157 g, 0.35 mol) and CH_2Cl_2 (700 ml). When $^1/_3$ of the acyl chloride was added, the product began to precipitate. After 4 h, the solvent was evaporated and the residue recrystallized from MeOH (180 ml; 48 h, −20°): 141.9 g (81%) of **1**, colourless crystalls. M.p. 238–239°. IR (KBr): 3440 (br.), 1758, 1748, 1693, 1588, 1530, 1488, 1433, 1348. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.04 (br., 1 H); 3.49 (*s*, 2 H); 3.65 (*s*, 3 H); 5.58 (*d*, J = 15, 2 H); 6.78–7.85 (*m*, 19 arom. H). Anal. calc. for $C_{29}H_{27}BrNO_3P$ (548.42): C 63.51, H 4.96, N 2.55; found: C 63.27, H 5.28, N 2.52.

2. *Methyl 1*H*-Indole-2-acetate* (**2**). A 1.95N soln. of sodium *tert*-pentylate in toluene (61.5 ml), diluted with toluene (60 ml), was added dropwise within 15 min to an intensively stirred suspension of **1** (67.5 g, 0.12 mol) in toluene (300 ml). The mixture was refluxed for 3 h, filtrated, evaporated to $^1/_4$ of its volume, and extracted with H_2O (3 × 50 ml). Then, the soln. was dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel (400 g) with hexane/CH_2Cl_2/AcOEt 4:2:1: **2** (15.8 g, 69.6%). M.p. 68–71° (Et_2O/hexane). The mother liquor was purified by bulb-to-bulb distillation: **2** (0.6 g, 2.6%). M.p. 68–69° (Et_2O/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.74 (*s*, 3 H); 3.83 (*s*, 2 H); 6.35 (*s*, 1 H); 7.02–7.62 (*m*, 4 arom. H); 8.64 (br. *s*, 1 H). Anal. calc. for $C_{11}H_{11}NO_2$ (189.14): C 69.83, H 5.86, N 7.40; found: C 69.58, H 5.92, N 7.28.

3. *Methyl 3-[(*E*)-2-Nitroethenyl]-1*H*-indole-2-acetate* (**4**). To a stirred soln. of *N,N*-dimethyl-2-nitroethenamine (**3**; 6.39 g, 55 mmol) in CH_2Cl_2 (50 ml), CF_3COOH (10 ml) was added dropwise at 0°, followed by a soln. of **2** (9.46 g, 50 mmol) in CH_2Cl_2 (100 ml). Stirring was continued at 0° for 1 h and then at 20° for 6 h. The mixture was cooled to −15°, and the yellow precipitate was collected by filtration and washed with CH_2Cl_2 (−20°) and Et_2O: **4** (10.4 g, 79.9%). M.p. 160–163°. From the mother liquor, after partial evaporation and chilling, a second crop of **4** (1.5 g, 11.5%) crystallized. M.p. 157–160. UV/VS (EtOH): 222.4 (4.35), 279.5 (4.02), 403.7 (4.31). IR (KBr): 3347, 1729, 1614, 1479. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.84 (*s*, 3 H); 4.07 (*s*, 2 H); 7.29–7.78 (*m*, 4 arom. H); 7.81 (*d*, J = 13.2, 1 H); 8.27 (*d*, J = 13.2, 1 H); 9.74 (br. *s*, 1 H). Anal. calc. for $C_{13}H_{12}N_2O_4$ (260.25): C 60.00, H 4.64, N 10.76; found: C 59.62, H 4.93, N 10.74.

4. *Methyl 3-(2- Nitroethyl)-1*H*-indole-2-acetate* (**5a**). 4.1. *Reduction of* **4** *with* **8**. A mixture of **4** (3.9 g, 15 mmol), **8** (5.16 g, 20 mmol), silica gel (0.063–0.200 mm; 1.5 g), and benzene (130 ml) was refluxed under N_2 for 25 h. The yellowish soln. was filtrated and evaporated and the residue chromatographed with hexane/CH_2Cl_2/AcOEt 3:1:1 over silica gel (200 g): 2.2 g (55.9%) of **5a**. M.p. 77° (Et_2O/pentane). Filtration of the residue of the mother liquor in CH_2Cl_2 through a column of silica gel (35 g) gave 340 mg (8.6%) of pure **5a**. IR (KBr): 3351, 1726, 1544. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.45 (*t*, J = 7.3, 2 H); 3.76 (*s*, 3 H); 3.83 (*s*, 2 H); 4.62 (*t*, J = 7.3, 2 H); 7.03–7.53 (4 arom. H); 8.65 (br. *s*, 1 H). Anal. calc. for $C_{13}H_{14}N_2O_4$ (262.27): C 59.54, H 5.38, N 10.68; found: C 59.17, H 5.23, N 10.77.

4.2. *Catalytic Hydrogenation of* **4**. The mixture of **4** (500 mg, 1.9 mmol), benzene (10 ml), and bis(triphenylphosphine)rhodium(I) chloride (*Fluka;* 50 mg) was stirred under H_2 (10 bar) at 50° for 16 h and subsequently evaporated. The residue was filtrated with hexane/CH_2Cl_2/AcOEt 2:1:1 over silica gel (15 g): 470 mg (93.3%) of pure **5a**.

5. *Isopropyl 3-(2-Nitroethyl)-1H-indole-2-acetate* (**5b**). The mixture of **5a** (530 mg, 2.05 mmol), i-PrOH (20 ml), and tetraisopropyl orthotitanate (1 ml) was refluxed for 17 h and subsequently evaporated. To the soln. of the residue in Et_2O (20 ml), 3N HCl was added dropwise until the precipitate formed was dissolved again. The Et_2O layer was washed with H_2O and sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The residue was crystallized from Et_2O/hexane: **5b** (542 mg, 91%). M.p. 75–76°. IR (CCl_4): 3440, 1730, 1555, 1462. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.27 (*d*, *J* = 6.3, 6 H); 3.43 (*t*, *J* = 7.5, 2 H); 3.76 (*s*, 2 H); 4.60 (*t*, *J* = 7.5, 2 H); 5.06 (*sept.*, *J* = 6.3, 1 H); 7.06–7.52 (*m*, 4 arom. H); 8.75 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{18}N_2O_4$ (290.32): C 62.06, H 6.25, N 9.65; found: C 62.14, H 6.03, N 9.55.

6. *Methyl 3-(2-Aminoethyl)-1H-indole-2-acetate* (**6a**). At 0°, **5a** (264 mg, 1.01 mmol) in MeOH (10 ml) was hydrogenated over Pd/C (0.2 g). After 3½ h, the catalyst was removed by filtration under N_2, the filtrate evaporated at 20°, and the residue dissolved in benzene and evaporated again: 230 mg (*ca.* 100%) of **6a**, which crystallized on treatment with Et_2O, but could not be recrystallized without decomposition. M.p. 57–58° (Et_2O). IR (KBr): 3355, 3287, 3146, 3055, 2994, 2840, 2732, 1794, 1436, 1307, 1242, 1184, 1010, 744. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.60 (*s*, NH_2, H_2O); 2.84–3.03 (*m*, 4 H); 3.74 (*s*, 3 H); 3.84 (*s*, 2 H); 7.06–7.58 (*m*, 4 arom. H); 8.54 (*s*, 1 H). MS: 232 (12, M^+), 203 (73), 202 (81), 144 (49), 142 (100).

7. *Isopropyl 3-(2-Aminoethyl)-1H-indole-2-acetate* (**6b**). As in *Exper. 6*, but at r.t. with **5b** (2.4 g, 8.3 mmol), MeOH (15 ml), and Pd/C (0.7 g) for 1½ h. The filtrate was evaporated to dryness: 2.13 g (*ca.* 100%) of **6**, colourless oil. A sample was crystallized from Et_2O/hexane. M.p. 97–99°. IR (CCl_4): 3443, 1728, 1460. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24 (*d*, *J* = 6.3, 6 H); 1.85 (br. *s*, 1 H); 2.80–3.04 (*m*, 4 H); 3.76 (*s*, 2 H); 5.03 (*sept.*, *J* = 6.3, 1 H); 7.02–7.60 (*m*, 4 arom. H); 8.90 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{20}N_2O_2$ (260.34): C 69.20, H 7.74, N 10.76; found: C 69.15, H 7.57, N 11.00.

8. *6,7,9,10-Tetrahydroazepino[4,5-b]indol-8(5H)-one* (**7**). A soln. of **6a** (79.6 mg, 0.34 mmol) in benzene (4 ml), after addition of a few mg of TsOH, was refluxed for 28 h. The mixture was evaporated and the soln. of the residue in CH_2Cl_2 washed with 0.1N HCl and H_2O (5 ml of each), dried ($MgSO_4$), and evaporated. The residue was crystallized from CH_2Cl_2/MeOH to afford 60 mg (88%) of **7**. M.p. > 230° (dec.). UV (EtOH): 222.5 (4.52), 283 (3.87), 290 (3.83). IR (KBr): 3376, 3297, 3199, 3081, 1663, 1461, 1406, 1352, 1306, 1231, 1135, 948, 801, 751. ^{1}H-NMR (250 MHz, (D_6)DMSO): 2.72–2.82 (*m*, 2 H); 3.49–3.60 (*m*, 2 H); 3.78 (*s*, 2 H); 6.90–7.39 (*m*, 4 arom. H); 7.78 (*t*, 1 H); 10.80 (*s*, 1 H). MS: 200 (100, M^+), 156 (17), 144 (79), 143 (90), 115 (17). Anal. calc. for $C_{12}H_{12}N_2O$ (200.24): C 71.98, H 6.04, N 13.99; found: C 71.51, H 6.10, N 13.90.

9. *Methyl (1RS,2SR,3SR,4SR)-2,3,4,9-Tetrahydro-2-{2-[(methoxycarbonyl)methyl]-1H-indol-3-yl}-3-nitro-4-(nitromethyl)-1H-carbazole-1-carboxylate* (**9**). After elution of **5a**, the chromatography described in *Exper. 4* was continued with CH_2Cl_2 to afford **9** (0.9 g, 23%). M.p. 215–216° (CH_2Cl_2/pentane). The substance contained 0.45 mol of CH_2Cl_2, which could not be removed on drying *i.v.* up to 100°. UV (EtOH): 218.7 (4.84), 281.5 (4.21), 289.2 (4.13). IR (KBr): 3415, 3392, 1795, 1555, 1458. ^{1}H-NMR (400 MHz, (D_6)DMSO)[6]: 3.55 (*s*, 3 H); 3.67 (*s*, 3 H); 3.83 (*d*, *J* = 18, 1 H); 3.95 (*d*, *J* = 18, 1 H); 4.43–4.42 (*m*, 1 H); 4.50 (*d*, *J* = 10, 1 H); 4.76–4.83 (*m*, 1 H); 4.98 (*dd*, *J* = 15.4, 3.7, 1 H); 5.31 (*dd*, *J* = 15.4, 8.6, 1 H); 6.14 (*dd*, *J* = 12, 4.8, 1 H); 6.90–7.76 (*m*, 8 arom. H). MS: 520 (12, M^+), 270 (40), 238 (66), 214 (68), 189 (71), 130 (100). Anal. calc. for $C_{26}H_{24}N_4O_8 \cdot 0.45\ CH_2Cl_2$ (558.72): C 56.86, H 4.49, N 10.03, Cl 5.71; found: C 56.94, H 4.68, N 9.93, Cl 5.58.

10. *Dimethyl 2-[(2-Nitrophenyl)acetyl]propanedioate* (**10a**). Mg turnings (5.35 g, 0.22 mol), MeOH (32 g, 1 mol), CCl_4 (1 ml), and dimethyl propanedioate (29.1 g, 0.22 mol) were reacted under carefully dried N_2 as follows: the reaction was started by injection of MeOH (5 ml) and CCl_4 (0.1 ml) to the Mg and kept going by slowly adding dropwise further MeOH. When it became slow, abs. THF (10 ml) and CCl_4 were added in small portions until all Mg was dissolved. Subsequently, the dimethyl propanedioate was slowly added. The mixture was transferred under N_2 pressure into a round-bottom flask, followed by THF (3 × 50 ml), and evaporated. The residue was dissolved in THF (100 ml), and a freshly prepared [13] (2-nitrophenyl)acetyl chloride (0.2 mol) soln. in Et_2O (100 ml) was slowly added. The mixture was refluxed for 15 min, chilled, and poured into a mixture of 2N H_2SO_4 (130 ml) and ice (50 g). The H_2O layer was extracted with Et_2O (2 × 100 ml) and the combined org. layer extracted first with sat. $NaHCO_3$ soln. (7 × 50 ml), then with 2N Na_2CO_3 (7 × 100 ml). The combined Na_2CO_3 layer was saturated with CO_2 (gas) and extracted with CH_2Cl_2 (7 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated: 47.2 g (80%) of crude **10a**. Crystallization from Et_2O (200 ml) after treatment with *Carboraffin* afforded 43 g (72.9%) of pale

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[6]) Amorphous substance, obtained by evaporation of a chromatographic fraction.

yellow **10a**. M.p. 71°. Workup of the mother liquor gave further 2 g (7%) of **10a**. ^{1}H-NMR (250 MHz, $CDCl_3$)[7]: 3.80, 3.84, 3.85 (3 *s*, together 6 H); 4.32, 4.38 (2 *s*, together 2 H); 4.73 (*s*, 0.5 H); 7.6–8.2 (4 arom. H); 13.92 (*s*, 0.5 H). Anal. calc. for $C_{13}H_{13}NO_7$ (295.25): C 52.89, H 4.44, N 4.74; found: C 52.97, H 4.67, N 4.80.

11. *Dimethyl 2-(1*H*-Indol-2-yl)propanedioate* (**11a**). A soln. of **10a** (11.81 g, 40 mmol) in MeOH (180 ml) was hydrogenated over Pd/C (0.5 g). After consumption of 2.7 l of H_2, the catalyst was removed by filtration under N_2 and the filtrate evaporated. The residue in MeOH (30 ml) was cooled with dry ice: 6.3 g of crystalline **11a**. M.p. 67–68°[8]). The mother liquor was evaporated and the residue crystallized from MeOH/H_2O: 1.7 g **11a**. M.p. 66–68°. Total yield 8 g (80.9%). IR (KBr): 3400, 1751, 1728, 1685, 1616, 1584, 1297, 1281, 1238. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.79 (*s*, 6 H); 4.95 (*s*, 1 H); 6.5 (*m*, 1 H); 7.06–7.60 (4 arom. H); 8.97 (*s*, 1 H). Anal. calc. for $C_{13}H_{13}NO_4$ (247.25): C 63.15, H 5.30, N 5.67; found: C 62.91, H 5.26, N 5.64.

On chromatography of crude **11a** (3 g) over SiO_2 (110 g) with $CHCl_3$, the tautomer **12** was eluated first: 150 mg. M.p. 84–85° (MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.81 and 3.84 (2 *s*, together 6 H); 4.35 (*s*, 2 H); 6.96–7.42 (4 arom. H); 11.51 (*s*, 1 H).

12. *Diisopropyl 2-(1*H*-Indol-2-yl)propanedioate* (**11c**). As in *Exper. 5*, with **11a** (12.36 g, 50 mmol) in i-PrOH (180 ml) at 0° and tetraisopropyl orthotitanate (14.2 ml), followed by refluxing for 24 h (Et_2O (300 ml) for workup). The residue crystallized on treatment with hexane (*ca.* 10 ml): 13.7 g (90%) of **11c**. M.p. 79–80°. IR ($CHCl_3$): 3450, 1730. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.14–1.42 (*m*, 12 H); 4.84 (*s*, 1 H); 5.09 (*sept.*, J = 7, 2 H); 6.48 (*m*, 1 H); 7.04–7.60 (4 arom. H); 9.04 (*s*, 1 H). MS: 304 (20), 303 (100, $M^{+\cdot}$), 217 (15), 216 (82), 175 (20), 174 (78), 157 (30), 156 (38), 129 (13), 128 (18), 43 (49), 41 (18). Anal. calc. for $C_{17}H_{21}NO_4$ (303.36): C 67.30, H 6.98, N 4.62; found: C 67.56, H 7.24, N 4.48.

13. *2-(Benzyloxy)ethyl Iodide* (**14**). A 0.936 N soln. of K(*t*-BuO) in *t*-BuOH (534 ml, 0.5 mol) was added dropwise to ethylene glycol (62 g, 1 mol). After 1 ½ h, the solvent was evaporated, the residue stirred with dioxane (200 ml), and benzyl chloride (63.3 g, 0.5 mol) slowly added. The mixture was stirred at 55° for 22 h. After evaporation, the residue was treated with H_2O and Et_2O, the aq. soln. brought to pH 6 by addition of 2 N H_2SO_4 and extracted twice with Et_2O, the combined org. phase dried ($MgSO_4$) and evaporated (74.1 g), and the brown oil distilled *in vacuo*: 53.4 g (70%) of *2-(benzyloxy)ethanol*. B.p. 70–83°/0.1 Torr.

To a mixture of 2-(benzyloxy)ethanol (30.4 g, 0.2 mol), Et_3N (24.2 g, 0.24 mol), and THF (200 ml) at *ca.* −40°, mesyl chloride (27.4 g, 0.24 mol) was added dropwise by syringe. The mixture was evaporated to ½ of its volume, cooled to −10°, and treated with ice/H_2O (100 g) and Et_2O (100 ml). The aq. layer was extracted with Et_2O (2 × 50 ml) and the combined org. phase dried ($MgSO_4$) and evaporated: 47.3 g (*ca.* 100%) of crude mesylate (yellowish oil). A mixture of this material with MeCN (300 ml) and NaI (60 g, 0.4 mol) was stirred at reflux temp. for 6 h, then cooled to r.t., and filtrated. The filtrate was evaporated and treated with H_2O (100 ml) and CH_2Cl_2 (50 ml). To remove free I_2, a small amount of Na_2SO_3 was added. The aq. layer was extracted with CH_2Cl_2 (50 ml), the combined org. layer dried ($MgSO_4$) and evaporated (51.3 g), and the crude product purified by fractional distillation to afford **14** (46.5 g, 88.7%). B.p. 83–87°/0.5 Torr. Identical with the compound described [14].

14. *Dimethyl 2-[3-(2-Hydroxyethyl)-1*H*-indol-2-yl]propanedioate* (**16**). The soln. of lithium bis(trimethylsilyl)amide (from hexamethyldisilazane (38.8 g, 0.24 mol) in THF (100 ml) and 1.6 N BuLi in hexane (155 ml, 0.248 mol)) was slowly added at −65° to a soln. of **11a** (24.7 g, 0.1 mol) in THF (200 ml). The stirred mixture was warmed to 20°. Then, **14** (31.4 g, 0.12 mol) was added, the mixture refluxed for 21 h, then cooled down to −10°, and acidified with 2 N H_2SO_4. The aq. layer was extracted with Et_2O (3 × 100 ml), the combined org. soln. dried ($MgSO_4$) and evaporated, and the crude product (45.6 g) chromatographed on silica gel (600 g) with hexane/CH_2Cl_2/AcOEt 40:20:3 (fractions of 150–300 ml each): 26.8 g of crude **15** as yellowish oil. This material was hydrogenated in MeOH/AcOH 9:1 (250 ml) over Pd/C (4.5 g): H_2 consumption 1.58 l. Then, the catalyst was removed by filtration under N_2 and the filtrate evaporated: 21.8 g of crude **16**. This material was purified by chromatography on silica gel (450 g); column preparation with hexane/CH_2Cl_2/AcOEt 4:1:1, substance application in hexane/CH_2Cl_2/AcOEt 3:1:1). First unpolar impurities were eluted with a 4:1:1 mixture, afterwards **16** with a 2:1:1 mixture. The crude **16** was crystallized from Et_2O: 5.2 g of m.p. 82–84°, then 3.1 g of m.p. 81–82° (together 57.3%). UV (EtOH): 220.9 (4.52), 283.5 (3.99), 291.9 (3.90). IR (KBr): 3549, 3426, 3361, 1752, 1730, 1710. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.66 (br. *s*, 1 H); 3.02 (*t*, J = 5.9, 2 H); 3.79 (*s*, 6 H); 3.9 (*t*, J = 5.6, 2 H); 5.10 (*s*, 1 H); 7.08–7.60 (*m*, 4 arom. H); 8.86 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{17}NO_5$ (291.03): C 61.85, H 5.88, N 4.81; found: C 61.76, H 6.08, N 5.04.

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[7]) Mixture of tautomers.

[8]) In other experiments, mixtures **11a**/**12** were obtained in crystalline form. M.p.'s between 66 and 78° were observed.

15. *Dimethyl 2-[3-(2-Iodoethyl)-1H-indol-2-yl]propanedioate* (**18**). To a soln. of **16** (4.37 g, 15 mmol) and *Hünig*'s base ($(i\text{-}Pr)_2EtN$; 2.13 g, 16.5 mmol) in THF (40 ml) at –45°, mesyl chloride (2.43 g, 16.5 mmol) in CH_2Cl_2 (15 ml) was added dropwise. The mixture was warmed to 0° within 2 h and then evaporated, the residue dissolved in CH_2Cl_2 (25 ml) and extracted with sat. $NaHCO_3$ soln. (2 × 10 ml), and the org. layer dried ($MgSO_4$) and evaporated. To the crude mesylate in MeCN (50 ml), NaI (3.38 g, 22.5 mmol) was added. The mixture was stirred at 70° for 3 h, cooled to r.t., and filtrated. The filtrate was evaporated, the residue treated with H_2O (50 ml), CH_2Cl_2 (50 ml), and a few mg of Na_2SO_3, and the org. layer washed with sat. $NaHCO_3$ soln. (25 ml), dried ($MgSO_4$), and evaporated. Crystallization of the residue gave **18** (4.5 g, 74.8%). M.p. 128–129° (Et_2O). From the mother liquor, a further crop (0.47 g, 7.8%) could be isolated by fractional crystallization. M.p. 125–129°. An anal. sample was obtained by recrystallization. M.p. 131–133° (Et_2O). ^{1}H-NMR (250 MHz, (D_6)DMSO): 3.36 (*s*(!), 4 H); 3.79 (*s*, 6 H); 5.03 (*s*, 1 H); 7.01–7.56 (*m*, 4 arom. H); 8.98 (*s*, 1 H). MS: 401 (33, M^+), 342 (7), 274 (100), 214 (26), 183 (25), 154 (53). Anal. calc. for $C_{15}H_{16}INO_4$ (401.20): C 44.91, H 4.02, N 3.49; found: C 45.17, H 4.08, N 3.49.

16. *Dimethyl 2-[3-(2-Azidoethyl)-1H-indol-2-yl]propanedioate* (**19a**). To a stirred soln. of LiN_3 (1.1 g, 22.5 mmol) in DMSO (15 ml) at 45°, **18** (1.61 g, 4.01 mmol) was added. After 1.5 h, the soln. was evaporated at 0.1 Torr and the residue treated with CH_2Cl_2 (10 ml) and H_2O (10 ml). The org. layer was extracted with sat. $NaHCO_3$ soln., dried (K_2CO_3), and evaporated. The crude **19a** was dissolved in Et_2O/hexane 1:1 (5 ml) and a little CH_2Cl_2 and filtrated through a column of silica gel (10 g) with Et_2O/hexane 1:1. Evaporation afforded 1 g (87.7%) of pure **19a** as a colourless, viscous oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.03 (*t*, J = 7.2, 2 H); 3.52 (*t*, J = 7.2, 2 H); 3.79 (*s*, 6 H); 5.06 (*s*, 1 H); 7.08–7.64 (*m*, 4 arom. H); 8.79 (br. *s*, 1 H).

17. *Diisopropyl 2-[3-(2-Azidoethyl)-1H-indol-2-yl]propanedioate* (**19b**). As in *Exper. 5*, with **19a** (248.5 mg, 0.79 mmol), i-PrOH (15 ml), and tetraisopropyl orthotitanate (0.3 g; refluxing for 16 h): 293 mg of crude **19b**. Crystallization (hexane/Et_2O 3:1) gave pure **19b** (243 mg, 82.6%). M.p. 66–68°. IR (KBr): 3373, 2098, 1749, 1700, 1459. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.26 (*d*, J = 5, 6 H); 1,28 (*d*, J = 5, 6 H); 3.04 (*t*, J = 3, 2 H); 3.51 (*t*, J = 3, 2 H); 4.94 (*s*, 1 H); 5.03–5.13 (*m*, 2 H); 7.08–7.60 (*m*, 4 arom. H); 9.05 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{24}N_4O_4$ (372.43): C 61.28, H 6.50, N 15.04; found: C 61.15, H 6.36, N 14.93.

18. *Dimethyl 2-[3-(2-aminoethyl)-1H-indol-2-yl]propanedioate* (**20a**). Azide **19a** (316 mg, 1 mmol) in MeOH (10 ml) was hydrogenated at 0° over Pd/C (0.34 g). After 3½ h, no **19a** was detectable by TLC. The catalyst was removed by filtration under N_2, the filtrate evaporated at 20°, and the residue dissolved in benzene and evaporated again: 260 mg (89.6%) of amorphous **20a**, containing *ca.* 15% of **21** (see *Exper. 20*). Crystallization from Et_2O/pentane gave again **20a**/**21**. ^{1}H-NMR of the main component (400 MHz, $CDCl_3$): 1.83 (*s*, NH_2, H_2O); 2.92 (*ca. t*, J = 6.6, 2 H); 3.00 (*ca. t*, J = 6.6, 2 H); 3.76 (*s*, 3 H); 5.10 (*s*, 1 H); 7.07–7.61 (*m*, 4 arom. H); 8.89 (*s*, 1 H).

19. *Diisopropyl 2-[3-(2-Aminoethyl)-1H-indol-2-yl]propanedioate* (**20b**). 19.1. *From* **19b**. At r.t., **19b** (374 mg, 1 mmol) was hydrogenated in i-PrOH (10 ml) over Pd/C (150 mg) for 6 h. The catalyst was removed by filtration under N_2 and the filtrate evaporated. The residue was crystallized from Et_2O/hexane: 312 mg (90%) of **20b**. M.p. 90°.

19.2. *From* **23**. At 40°, **23** (5 g, 13.3 mmol) was hydrogenated in i-PrOH (100 ml) over Pd/C (1.1 g). The catalyst was removed by filtration under N_2 and the filtrate evaporated. The residue was crystallized from Et_2O/hexane: 4.05 g (88%) of **20b**. M.p. 90°. IR (CCl_4): 3450, 1748, 1730. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.17–1.38 (*m*, 12 H); 1.82 (br. *s*, 2 H); 2.8–3.4 (*m*, 4 H); 4.97 (*s*, 1 H); 5.07 (*sept.*, J = 6.3, 2 H); 7.01–7.62 (*m*, 4 H); 8.95 (*s*, 1 H). CI-MS: 347 ($[M + 1]^+$). Anal. calc. for $C_{19}H_{26}N_2O_4$ (346.43): C 65.87, H 7.56, N 8.09; found: C 65.84, H 7.84, N 8.34.

20. *Methyl 5,6,7,8,9,10-Hexahydro-8-oxoazepino[4,5-b]indole-9-carboxylate* (**21**). Crystalline **20a** (36 mg, 0.12 mmol) was suspended in H_2O (3 ml) and 1N HCl added dropwise under stirring (→pH 2). After 10 min, the precipitate was isolated by filtration and washed with H_2O: 27.5 mg (86.6%) of pure **21**. M.p. 190° (dec.). IR (KBr): 3368, 1727, 1660, 1460, 1432, 1298, 1008, 745. ^{1}H-NMR (250 MHz, (D_6)DMSO): 2.64–2.92 (*m*, 2 H); 3.34–3.42 (*m*, 2 H); 3.72 (*s*, 3 H); 4.78 (*s*, 1 H); 6.96–7.48 (*m*, 4 arom. H); 8.1 (br. *t*, 1 H); 10.87 (*s*, 1 H). MS: 258 (70, M^+), 226 (37), 202 (53), 170 (100), 156 (23), 142 (27), 115 (27). Anal. calc. for $C_{14}H_{14}N_2O_3$ (258.28): C 65.11, H 5.46, N 10.85; found: C 64.83, H 5.51, N 10.80.

21. *Diisopropyl 2-{3-[(E)-2-Nitroethenyl]indol-2-yl}propanedioate* (**22**). A soln. of CF_3COOH (8.1 ml) in CH_2Cl_2 (15 ml) was slowly added at 0° to a soln. of **3** (4.88 g, 42 mmol) in CH_2Cl_2 (40 ml), followed by a soln. of **11c** (12.1 g, 40 mmol) in CH_2Cl_2 (40 ml). After stirring for 5 h at 0° and 4 h at r.t., the mixture was cooled to 0°, treated with ice and 2N Na_2CO_3 (pH→8) and extracted twice with CH_2Cl_2. The combined org. layer were washed with brine, dried ($MgSO_4$), and filtrated through a column of silica gel (120 g). Evaporation afforded **22** (12.7 g, 84.8%) as yellow crystals. A sample was recrystallized from MeOH. M.p. 178°. IR (KBr): 3350, 1750, 1718, 1625,

1502, 1495, 1462, 1325, 1297, 1268. ^{1}H-NMR ($CDCl_3$): 1.07–1.21 (*m*, 12 H); 5.00–5.22 (*m*, 2 H); 5.17 (*s*, 1 H); 7.24–7.80 (*m*, 4 arom H); 7.85 (*d*, J = 13.4, 1 H); 8.35 (*d*, J = 13.4, 1 H); 10.11 (*s*, 1 H). CI-MS: 375 (100, $[M+1]^+$). Anal. calc. for $C_{19}H_{22}N_2O_6$ (374.39): C 60.95, H 5.92, N 7.48; found: C 60.70, H 5.69, N 7.20.

22. *Diisopropyl 2-[3-(2-Nitroethyl)indol-2-yl]propanedioate* (**23**). To a stirred soln. of **22** (13.1 g, 35 mmol) in $CHCl_3$ (560 ml) and i-PrOH (70 ml) under N_2, silica gel (70 g) and, subsequently in small portions, $NaBH_4$ (5.5 g, 0.15 mol) were added. After 18 h, the excess of $NaBH_4$ was destroyed by addition of 3 N HCl and the unsoluble removed by filtration (all H_2O was adsorbed to the silica gel). The filtrate was washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated, and the residue in CH_2Cl_2 filtered over silica gel (120 g). The filtrate was evaporated and the residue crystallized: 8.6 g (65.3%) of **23**. M.p. 87–88° (CH_2Cl_2/hexane). From the mother liquor, further 1.8 g (13.7%) of **23** were isolated, after chromatography with hexane/$CHCl_3$/AcOEt 4:2:1 over silica gel (200 g). IR (KBr): 3570, 1745, 1728, 1552, 1460, 1377, 1100. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.08–1.18 (*m*, 12 H); 3.49 (*t*, J = 7.3, 2 H); 4.63 (*t*, J = 7.3, 2 H); 4.93 (*s*, 1 H); 5.08 (*sept.*, J = 6.3, 2 H); 7.08–7.64 (*m*, 4 arom. H); 9.16 (*s*, 1 H). MS: 376 ($M^{+\cdot}$). Anal. calc. for $C_{19}H_{24}N_2O_6$ (376.40): C 60.62, H 6.43, N 7.44; found: C 60.36, H 6.46, N 7.57.

REFERENCES

[1] a) K. Pfoertner, K. Bernauer, *Helv. Chim. Acta* **1968,** *51,* 1787; b) S. Mahboobi, K. Bernauer, unpublished.

[2] W.A. Remers, in 'Heterocyclic Compounds', Ed. W.J. Houlihan, J. Wiley & Sons, Inc., New York, 1972, Vol. 25, p. 1.

[3] R.A. Jones, in 'Comprehensive Heterocyclic Chemistry', Ed. A.R. Katrizky, Pergamon Press, Oxford, 1984, Vol. 4, p. 201.

[4] W. Schindler, *Helv. Chim. Acta* **1958,** *41,* 1441.

[5] K.S. Bhandari, V. Snieckus, *Can. J. Chem.* **1971,** *49,* 2354.

[6] L. Capuano, A. Ahlhelm, H. Hartmann, *Chem. Ber.* **1986,** *119,* 2069.

[7] G. Büchi, C.-P. Mak, *J. Org. Chem.* **1977,** *42,* 1784.

[8] K. Nakamura, M. Fujii, S. Oka, A. Ohno, *Chem. Lett.* **1985,** 523.

[9] J.H. Teuber, D. Cornelius, U. Wölke, *Liebigs Ann. Chem.* **1966,** *696,* 116; S. Naruto, O. Yonemitsu, *Chem. Pharm. Bull.* **1980,** *28,* 900.

[10] D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, M. Züger, *Synthesis* **1982,** 138.

[11] R.K. Brown, in 'Heterocyclic Compounds', loc. cit. [2], p. 227.

[12] J. Gudjons, R. Oehl, P. Rosenmund, *Chem. Ber.* **1976,** *109,* 3282.

[13] Organic Synthesis, Coll. Vol. IV, 708.

[14] S.M. Ludemann, D.L. Bartlett, G. Zon, *J. Org. Chem.* **1979,** *44,* 1163.

[15] A.K. Sinhababu, R.T. Borchardt, *Tetrahedron Lett.* **1983,** *24,* 227.