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Synthesis and antiinflammatory activity of indolylacrylic and methylacrylic acids

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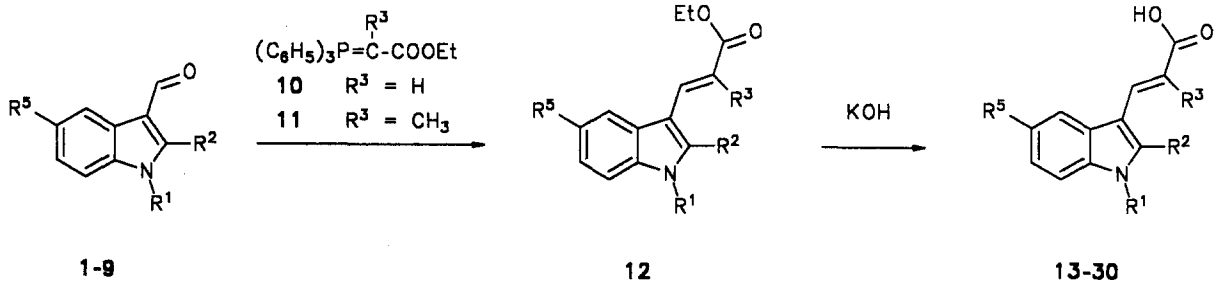
In pursuing our research on the synthesis of indole carboxylic acids as potential antiinflammatory/analgesic agents [1–4] we wish to describe here a new series of indolylacrylic and methylacrylic acids **13–30** (scheme 1). The aim of this work is to study the effect of 4 substituents on the antiinflammatory activity. The acrylic analogue of indomethacin has been described previously [5], and so R^2 was chosen to be different from CH_3 (H or Cl). It was also our purpose to prepare derivatives in which R^1 is a 4-chlorobenzoyl group but, under the experimental conditions employed, the indoles underwent cleavage of the amide bond with loss of the benzoyl group. As a result of this behaviour, compounds **29** and **30** (bearing a 4-chlorobenzyl group at position 1 and a methoxy group at position 5) are those which more closely resemble the structure of indomethacin.

Chemistry

The starting materials were the aldehydes **1–9** which were prepared according to the literature (see table I) except 2-chloro-1-(4-chlorobenzyl)-5-methoxyindole-3-carboxaldehyde **9** which was obtained by alkylating the sodium salt of 2-chloro-5-methoxyindole-3-carboxaldehyde with 4-chlorobenzyl chloride in DMF.

The aldehydes **1–9** were reacted under Wittig conditions with (carbethoxymethylene)triphenylphosphorane **10** or (carbethoxyethylidene)triphenylphosphorane **11**. The alkaline hydrolysis of the crude intermediate ester **12** thus obtained gave the indolylacrylic and methylacrylic acids **13–30**. Spectroscopic data for compounds **13–30** are reported in table II. These compounds belong to the *E* configuration like the analogues we reported previously [4]. In fact the



Scheme 1. Preparation of **13–30**. For definition of R^1R^5 see table I.

Table I. Compounds **13–30**.

Compound	R^1	R^2	R^3	R^5	*Starting aldehyde*	*Formula (mw)*	*Mp (°C) (solvent)*
13	H	H	H	H	**1**	$C_{11}H_9NO_2$ (187.2)	188–190 dec[a] (toluene)
14	H	H	CH_3	H	**1**	$C_{12}H_{11}NO_2$ (201.2)	222–225 dec (CH_3CN)
15	H	Cl	H	H	**2** [6]	$C_{11}H_8ClNO_2$ (221.6)	205–206 dec (EtOH)
16	H	Cl	CH_3	H	**2**	$C_{12}H_{10}ClNO_2$ (235.7)	149–152 dec ($EtOH/H_2O$)
17	CH_3	Cl	H	H	**3** [2]	$C_{12}H_{10}ClNO_2$ (235.7)	218–220 dec (EtOH)
18	CH_3	Cl	CH_3	H	**3**	$C_{13}H_{12}ClNO_2$ (249.7)	198–201 dec (EtOH)
19	C_6H_5	Cl	H	H	**4** [1]	$C_{17}H_{12}ClNO_2$ (297.7)	204–207 dec (EtOH)
20	C_6H_5	Cl	CH_3	H	**4**	$C_{18}H_{14}ClNO_2$ (311.8)	185–187 (pet ether)
21	$CH_2C_6H_5$	H	H	H	**5** [7]	$C_{18}H_{15}NO_2$ (277.3)	170–173 dec (EtOH)
22	$CH_2C_6H_5$	H	CH_3	H	**5**	$C_{19}H_{17}NO_2$ (291.3)	214–218 dec (EtOH)
23	$CH_2C_6H_5$	Cl	H	H	**6** [7]	$C_{18}H_{14}ClNO_2$ (311.8)	214–217 dec (EtOH)
24	$CH_2C_6H_5$	Cl	CH_3	H	**6**	$C_{19}H_{16}ClNO_2$ (325.8)	172–174 (EtOH)
25	$CH_2C_6H_4Cl(p)$	H	H	H	**7** [7]	$C_{18}H_{14}ClNO_2$ (311.8)	188–190 dec (CH_3CN)
26	$CH_2C_6H_4Cl(p)$	H	CH_3	H	**7**	$C_{19}H_{16}ClNO_2$ (325.8)	192–195 dec (EtOH)
27	$CH_2C_6H_4Cl(p)$	Cl	H	H	**8** [7]	$C_{18}H_{13}Cl_2NO_2$ (346.2)	243–245 dec (EtOH)
28	$CH_2C_6H_4Cl(p)$	Cl	CH_3	H	**8**	$C_{19}H_{15}Cl_2NO_2$ (360.2)	192–195 dec (EtOH)
29	$CH_2C_6H_4Cl(p)$	Cl	H	OCH_3	**9**	$C_{19}H_{15}Cl_2NO_3$ (376.2)	233–235 dec (EtOH)
30	$CH_2C_6H_4Cl(p)$	Cl	CH_3	OCH_3	**9**	$C_{20}H_{17}Cl_2NO_3$ (390.3)	176–180 (EtOH)

[a]Lit [8] mp 195–196°C.

coupling constants of the olefinic hydrogens in the acrylic acids **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27** and **29** (16 Hz) are typical for this configuration. In the methylacrylic acids (**14**, **16**, **18**, **20**, **22**, **24**, **26**, **28** and **30**), nuclear Overhauser enhancement (NOE) was not observed for the olefinic proton (7.5–7.9 ppm) when the methyl group (1.9–2.1 ppm) was saturated, thus confirming the *E* configuration.

Pharmacological results

Compounds **13–30** were tested in mice in the phenyl-*p*-benzoquinone-induced writhing test and in rats in the carrageenen paw edema test (see *Experimental protocols*). Only 2 compounds (**29** and **30**) gave a significant analgesic and antiinflammatory activity at 50 mg/kg *ip*. Compound **29** gave 55% (writhing) and 63% (carrageenen) protection. Under the same experimental conditions, compound **30** gave 60% and 44% protection, respectively.

Experimental protocols

Chemistry

The melting points were detected by an Electrothermal apparatus and are uncorrected. Analyses (C, H, N) were within ±0.4% of the theoretical values. Bakerflex plates (silica gel IB2-F) were used for TLC and Kieselgel 60 (Merck) for

Table II. IR and ^{1}H-NMR of compounds **13–30**.

Compound	ν_{max} *(cm^{-1})*[a]	*δ (ppm); J (Hz) in DMSO-d$_6$*[b, c]
13	1640, 1285, 1240, 735	6.31 (1H, d, CH, *J* = 16), 7.19 (2H, *m*, ind), 7.46 (1H, *d*, ind), 7.82 (1H, d, CH, *J* = 16), 7.84 (1H, *d*, ind), 7.91 (1H, s, H2), 11.72 (1H, s, NH)
14	1665, 1330, 1280, 750	2.09 (3H, s, CH_3), 7.15 (2H, *m*, ind), 7.46 (1H, *d*, ind), 7.70 (1H, *d*, ind), 7.75 (1H, s, H2), 7.93 (1H, s, CH), 11.79 (1H, s, NH)
15	1655, 1610, 1280, 1240	6.45 (1H, d, CH, *J* = 16), 7.22 (2H, *m*, ind), 7.41 (1H, *d*, ind), 7.72 (1H, d, CH, *J* = 16), 7.84 (1H, *d*, ind), 12.75 (1H, s, NH)
16	1665, 1415, 1270, 735	1.94 (3H, s, CH_3), 7.18 (2H, *m*, ind), 7.38 (1H, *d*, ind), 7.43 (1H, *d*, ind), 7.59 (1H, s, CH), 12.38 (1H, s, NH)
17	1670, 1620, 1290, 735	3.82 (3H, s, CH_3), 6.45 (1H, d, CH, *J* = 16), 7.26 (1H, *t*, ind), 7.33 (1H, *t*, ind), 7.61 (1H, *d*, ind), 7.74 (1H, d, CH, *J* = 16), 7.88 (1H, *d*, ind)
18	1680, 1630, 1280, 730	1.94 (3H, s, C-CH_3), 3.82 (3H, s, N-CH_3), 7.18 (1H, *t*, ind), 7.28 (1H, *t*, ind), 7.47 (1H, *d*, ind), 7.57 (1H, *d*, ind), 7.61 (1H, s, CH)
19	1675, 1615, 1595, 1290	6.58 (1H, d, CH, *J* = 16), 7.11 (1H, *d*, ind), 7.30 (2H, *m*, ind), 7.55 (2H, m, ar), 7.66 (3H, m, ar), 7.82 (1H, d, CH, *J* = 16), 7.99 (1H, *d*, ind)
20	1690, 1630, 1500, 735	1.98 (3H, s, CH_3), 7.10 (1H, *d*, ind), 7.23 (2H, *m*, ind), 7.60 (6H, m: 1H, ind + 5H, ar), 7.65 (1H, s, CH)
21	1670, 1600, 1280, 1160	5.47 (2H, s, CH_2), 6.34 (1H, d, CH, *J* = 16), 7.26 (7H, m: 2H, ind + 5H, ar), 7.56 (1H, *d*, ind), 7.81 (1H, d, CH, *J* = 16), 7.88 (1H, *d*, ind), 8.11 (1H, s, H2)
22	1665, 1525, 1325, 1275	2.12 (3H, s, CH_3), 5.53 (2H, s, CH_2), 7.18 (2H, *m*, ind), 7.28 (5H, *m*, ar), 7.50 (1H, *d*, ind), 7.73 (1H, *d*, ind), 7.92 (1H, s, CH), 8.03 (1H, s, H2)
23	1665, 1600, 1290, 740	5.59 (2H, s, CH_2), 6.51 (1H, d, CH, *J* = 16), 7.15 (2H, *m*, ind), 7.30 (5H, m, ar), 7.64 (1H, *d*, ind), 7.78 (1H, d, CH, *J* = 16), 7.93 (1H, *d*, ind)
24	1680, 1280, 1140, 735	1.94 (3H, s, CH_3), 5.57 (2H, s, CH_2), 7.15 (2H, *m*, ind), 7.28 (5H, m, ar), 7.49 (1H, *d*, ind), 7.59 (1H, *d*, ind), 7.62 (1H, s, CH)
25	1655, 1520, 1325, 1280	5.46 (2H, s, CH_2), 6.33 (1H, d, CH, *J* = 16), 7.21 (2H, *m*, ind), 7.26 (2H, d, ar, *J* = 8), 7.39 (2H, d, ar, *J* = 8), 7.53 (1H, *d*, ind), 7.79 (1H, d, CH, *J* = 16), 7.87 (1H, *d*, ind), 8.10 (1H, s, H2)
26	1650, 1320, 1275, 730	2.11 (3H, s, CH_3), 5.52 (2H, s, CH_2), 7.17 (2H, *m*, ind), 7.28 (2H, d, ar, *J* = 8), 7.38 (2H, d, ar, *J* = 8), 7.48 (1H, *d*, ind), 7.73 (1H, *d*, ind), 7.91 (1H, s, CH), 8.03 (1H, s, H2)
27	1670, 1600, 1285, 1190	5.58 (2H, s, CH_2), 6.51 (1H, d, CH, *J* = 16), 7.14 (2H, d, ar, *J* = 8), 7.28 (2H, *m*, ind), 7.38 (2H, d, ar, *J* = 8), 7.63 (1H, *d*, ind), 7.76 (1H, d, CH, *J* = 16), 7.92 (1H, *d*, ind)
28	1680, 1270, 1135, 730	1.93 (3H, s, CH_3), 5.56 (2H, s, CH_2), 7.14 (2H, d, ar, *J* = 8), 7.17 (1H, *t*, ind), 7.24 (1H, *t*, ind), 7.39 (2H, d, ar, *J* = 8), 7.48 (1H, *d*, ind), 7.58 (1H, *d*, ind) 7.60 (1H, s, CH)
29	1680, 1610, 1485, 1290	3.85 (3H, s, OCH_3), 5.55 (2H, s, CH_2), 6.48 (1H, d, CH, *J* = 16), 6.94 (1H, dd, H6, *J* = 2, *J* = 9), 7.13 (2H, d, ar, *J* = 8), 7.32 (1H, d, H4, *J* = 2), 7.40 (2H, d, ar, *J* = 8), 7.55 (1H, d, H7, *J* = 9), 7.77 (1H, d, CH, *J* = 16)
30	1670, 1615, 1280, 1230	1.92 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 5.52 (2H, s, CH_2), 6.86 (1H, dd, H6, *J* = 2, *J* = 9), 6.90 (1H, d, H4, *J* = 2), 7.11 (2H, d, ar, *J* = 8), 7.39 (2H, d, ar, *J* = 8), 7.48 (1H, d, H7, *J* = 9), 7.58 (1H, s, CH)

[a]The OH stretching vibrations of the carboxylic group are in the range 3200–2300 cm^{-1}; the NH stretching vibrations (**13–16**) in the range 3400–3300 cm^{-1}; [b]abbreviations: *d*, ind = H4 or H7; *t*, ind = H5 or H6; *m*, ind = H5 + H6; ar = aromatic; [c]the COOH group gives rise to a broad singlet in the range 11.9–12.6 ppm.

column chromatography. The eluent was a mixture of petroleum ether/acetone in various proportions. The IR spectra were recorded in nujol on a Perkin–Elmer 298. The ^{1}H-NMR spectra were recorded on a Varian Gemini (300 MHz) using TMS as the internal standard.

2-Chloro-1-(4-chlorobenzyl)-5-methoxyindole-3-carboxaldehyde ***9***

2-Chloro-5-methoxyindole-3-carboxaldehyde [9, 10] (14 mmol) was dissolved in dry DMF (25 ml) and treated portionwise, under stirring, with 20 mmol NaH (from a 50% dispersion in mineral oil, washed 3 times with 3 ml petroleum ether). The mixture was stirred at room temperature for 10 min and treated with 20 mmol of 4-chlorobenzyl chloride. After 1 h at 90°C under stirring, the mixture was poured onto ice. The resulting precipitate was collected by filtration and crystallized from ethanol with a yield of 70%. $C_{17}H_{13}Cl_2NO_2$ (334.2), mp 158–160°C; ν_{max} (cm^{-1}): 1650, 1485, 1270, 1230, 1040 1015, 850, 720; δ (ppm) in DMSO-d_6: 3.80 (3H, s, OCH_3), 5.59 (2H, s, CH_2), 6.96 (1H, dd, H6, J = 2 Hz, J = 9 Hz), 7.18 (2H, d, ar, J = 8 Hz), 7.41(2H, d, ar, J = 8 Hz), 7.58 (1H, d, H7, J = 9 Hz), 7.63 (1H, d, H4, J = 2 Hz), 10.01 (1H, s, CHO).

Synthesis of indolylacrylic and methylacrylic acids ***13–30***

The appropriate aldehyde (see table I) (20 mmol) was dissolved in CH_3CN (200 ml) and treated with 21 mmol (carbethoxymethylene)triphenylphosphorane **10** or (carbethoxyethylidene)-triphenylphosphorane **11**. The reaction mixture was refluxed for 9 h, the solvent was removed under reduced pressure and the residue treated with water. The ethylester thus obtained had the general formula **12**. It was not purified and characterized but was used as such in the following step (alkaline hydrolysis). The corresponding acid (**13–30**) was formed and was crystallized from the solvent reported in table I (compound **16** was first purified by means of column chromatography). The yield, calculated from the aldehyde, was 70–80%.

Pharmacology

Phenyl-p-benzoquinone (PQ)-induced writhing test in mice

The test compound, dissolved in dimethylsulfoxide or suspended in carboxymethylcellulose, was given intraperitoneally to 24-h fasted female mice (Swiss CD1, 20–25 g of body weight), divided into groups of 5–15 animals, 60 min before an ip injection of PQ (10 ml/kg of a 0.02% solution in 5% ethanol, corresponding to 2 mg/kg). The characteristic writhing responses (such as stretching, twisting a hind leg inward or contraction of the abdomen) were observed and counted in the group, from 5 to 15 min after PQ administration. Percentage protection from PQ effects was calculated as usual [11]: significant activity was considered to occur when the number of writhes was reduced by 50% compared with controls (% protection = 50). Indomethacin at 10 mg/kg gave 80% protection.

Carrageenen paw edema test in rats

Male Wistar rats weighing 130–140 g were used. They were fed on pellet chow and water *ad libitum*, and housed at a temperature of 22 ± 1°C and relative humidity of 55 ± 5%. After fasting for 16 h, the animals were assigned to groups by randomization. Paw edema [12] was induced in rats by a subplantar injection of 0.1 ml of 1% carrageenen suspension in saline into the right hind paw. The increase of paw volumes were measured 1, 3 and 5 h after the carrageenen injection. The percentage of inhibition was calculated from the difference in the swelling between the treated and the control group. The test compounds, suspended in 0.5% carboxymethylcellulose, were intraperitoneally injected 30 min before carrageenen. Indomethacin at 10 mg/kg ip gave 60% protection.

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