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Syntheses of the New Indole Derivatives Related to Indomethacin

M. Mihalić, V. Šunjić, F. Kajfež, V. Čaplar, and T. Kovač

Department of Biomedical and Biochemical Research, Compagnia di Ricerca Chimica, C R C, 33048 San Giovanni al Natisone (UD), Italy

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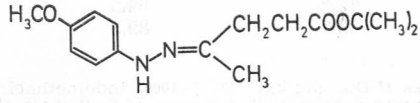
Syntheses and properties of the new indole derivatives **18—33**, being potential antiinflammatoric agents, are described. 1-*p*-Chlorobenzoyl-2-methyl-3-(2'-methyl-4'-nitroimidazol-1'-yl)-5-methoxyindole (**32**) have been found to possess pronounced antiinflammatoric activity and very low ulcerogenity. Attempting preparation of *N*-benzoylindole derivative **38** via sigmatropic rearrangement of the open chain precursor **35**, as a model procedure for the new synthesis of indomethacin, very low yields on the desired cyclic product **38** have inevitably been obtained.

INTRODUCTION

Since some earlier reports[1–3] claimed strong antiinflammatory activity for 1-(4-chlorobenzoyl)-2-methyl-5-methoxyindol-3-acetic acid (**1**, generic name: indomethacin), several groups have been exploring the field of polysubstituted *N*-acyl indoles, in order to find compounds with more beneficial therapeutic properties[4,5], or to find a new synthetic approach to indomethacin[6–7]. In this paper we describe our own efforts directed toward both these aims.

RESULTS AND DISCUSSION

Two entirely different synthetic approaches to *N*-benzoylated-2-methyl-3,5--disubstituted indoles have been investigated during the course of this work. The first was based on the classical Fischer-indole synthesis[8]. Introduction of the substituted-benzoyl group on N(1) was attempted at early stages of the synthesis, since some steps in the preparation of unacylated indoles gave low yields of the desired product, but several undesired side-products. Seemingly, the most attractive pathway was *p*-chlorobenzoylation of *N*(1)-(4-methoxyphenyl)-*N*(2)-t-butyl-levulinate hydrazone (**2**), which was prepared by a procedure used by Stevens et al.[9] in preparing a similar compound. Extensive experimentation, however, failed to show a way for *N*(1)-*p*-chlorobenzoylation[10] of this compound. Attempted mono-condensation of β-diketones with *p*-methoxyphenylhydrazine inevitably led to cyclization into pyrazoles **3** and **4**.



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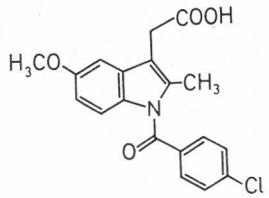

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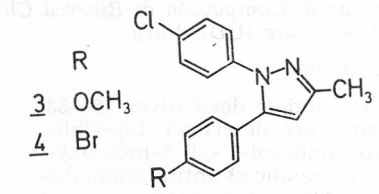
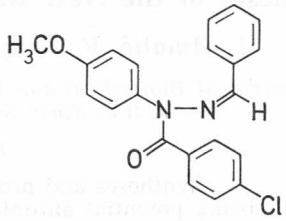


3 OCH_3

4 Br



5

Thereafter we turned to using benzaldehyde as a protecting group, and the *p*-methoxyphenylhydrazone thus obtained[11] was *p*-chlorobenzoylated into **5**. Among other spectroscopic and analytical supports for structure **5**, there was a hypsochromic shift of the two characteristic UV-bands at 352 and 320 nm, respectively, due to *N*(1)-benzoylation so that the benzoylated product possessed bands at 299 and 275 nm, respectively. The hydrolytic cleavage of the protecting group in **5** proved to be very cumbersome and lead to concomitant cleavage of the acyl group. Therefore we went over to acetaldehyde[7] as the protecting group, which allowed high yields of the *N*(1)-acyl-*N*(2)-hydrazones **6**—**11**, and their selective cleavage leading to hydrochlorides **12**—**17**. Most of these could be subsequently cyclized with β-diketones in glac. acetic acid, giving 1,3-diaroyl indoles **18**—**27**. Under similar cyclization conditions, indoles with various C(3)-substituents, **28**—**33**, have also been prepared.

Pharmacological screening of compounds **18**—**33** gave results showing that compound **32** compared most favorably with indomethacin in regard to analgetic power and low ulcerogenic activity[13].

TABLE I

Comparison of Analgetic Activities of **32**, *Indomethacin and Phenylbutazone in the Rat*

Dose[a] mg/kg	Relative Analgetic Activity[b]		
	32	Indomethacin	Phenylbutazone
5	35.2	33.2	—
10	60.1	54.3	—
25	72.3	64.5	—
50	103.7	89.3	42.0

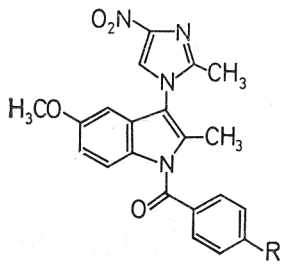
[a] Fifty-per cent lethal doses (LD_{50}, mg/kg): **32**: > 1000, indomethacin: 30, phenylbutazone: 1120.
[b] Relative analgetic activity was determined on groups of 6—10 male albino rats tested for responsiveness to pressure applied to a fixed point upon the noninflamed plantar surface of the foot. The experimental procedure followed was entirely those described by Randall and Selitto[13].

TABLE II

Comparison of Ulcerogenic Activity of Peroral **32** *and Indomethacin in the Rat*[a]

Compd. tested	Dose mg/kg	Number of animals affected in group
32	100	0/5
	200	0/5
	1000	0/5
Indome-thacin	2.5	0/5
	5.0	1/12
	10.0	6/6

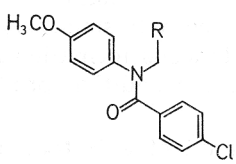
[a] Experimental method described in: G. Volterra, N. Pisanti, and A. Meli, *Proc. Soc. Exp. Biol. Med.* **146** (1974) 146.



	R
32	Cl
33	OCH_3

It is worth mentioning that high antiinflammatory activity found with **32**, when applying standard tests, is not connected with the presence of α-(hetero)--aryl acetic-, or propionic moiety, which are usually present in antiinflammatory substances[4,14]. The absence of such groups may account for the very low ulcerogenic activity of **32**, which is the most frequent side effect of other acidic antiinflammatory agents.

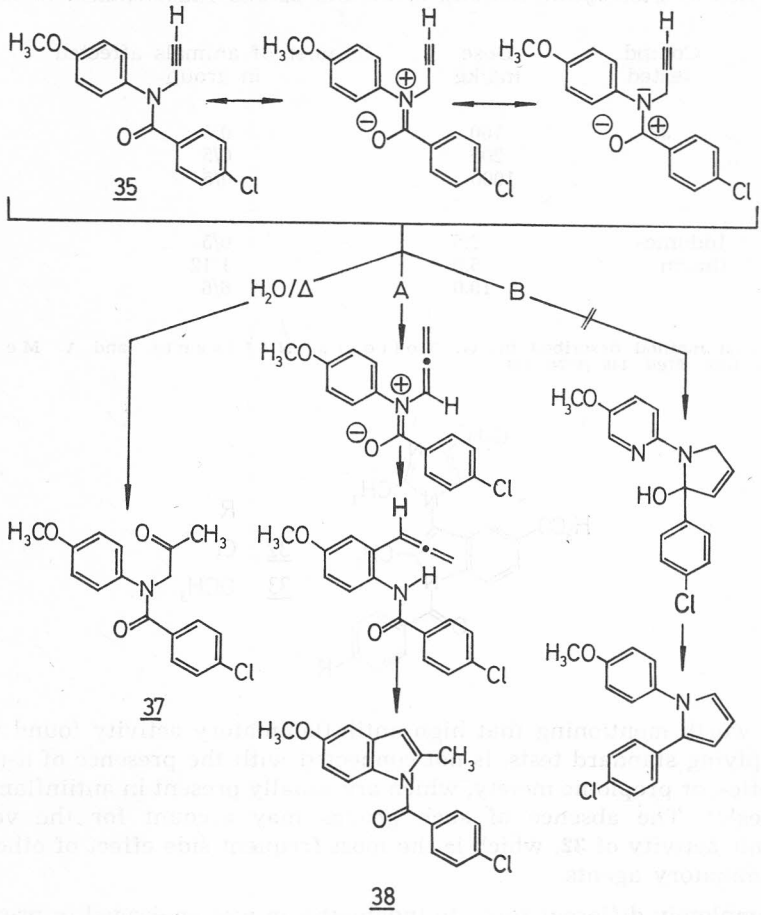
A completely different route to indomethacin was envisaged in preparation of compound **34**, and its cyclization accompanied by thermal 1,7-sigmatropic proton shift, and concomitant pyrolisis of the *tert.*-butyl group.



	R
34	$C{\equiv}C{-}CH_2{-}COOC(CH_3)_3$
35	$C{\equiv}CH$
36	$HC{=}CH_2$

Therefore, model cyclization reactions of **35** and **36** were investigated. We regarded the polar imide structures of these compounds both of which carry positive charges on the nitrogen atoms as being equivalent to protonated, or to Lewis-acid coordinated, alkyl anilines in the charge-induced sigmatropic rearrangements intensively studied by H. Schmid et al.[15,16].

SCHEME 1.



Of the two heterocycles presumed to form as the products of pathways A and B, only compound **38** has been isolated at a rather low yield. The product of pathway B was not isolated, although its formation was expected because similar products of cyclization were obtained with some *sec.*-propargyl amides[17]. Under more forcing conditions[15,16] simultaneous formation of **37** was observed. The latter can be formally regarded as the addition product of one mole of water to the triple bond in **35**.

Relating to the observation of Schmid et al.[16] that allyl-derivatives are generally more reactive than propargyl-derivatives in the charge-induced Claisen- and amino-Claisen rearrangements, we tried to cyclize **36** in sulfolane. In some experiments we introduced oxygen to oxidize the presumably formed 2,3-dihydro intermediary derivative of **38**. However, all attempts led to untractable mixtures of compounds, where *N*-debenzoylated products prevailed. Thus, we were forced to conclude that charge polarization in the *tert.*-amides **35** and

36 behaves not so activating by far as full-charge introduction in proton- or Lewis-acid catalysed amino-Claisen rearrangements[16].

EXPERIMENTAL

Melting points were determined on a Kofler-microheating stage and are uncorrected. NMR-spectra were obtained on spectrometers Varian T-60 and Perkin Elmer R 12A, using TMS as an internal standard; shifts are given as δ values in ppm. IR spectra were recorded on a Perkin Elmer M-257 spectrophotometer and are for KBr-pellets, unless stated otherwise. UV spectra were obtained on a Varian-Techtron UV-VIS M-635 automatic spectrophotometer. Column chromatography was run on silicagel 0.05—0.2 mm (Merck), fractions were collected automatically using a LKB 7000 Ultra Rac instrument, and monitored by TLC on silicagel F-254 plates (Merck), using an UV-254 nm lamp.

Starting materials. — *p*-Chloro- and *p*-methoxyphenylhydrazines[18] and their corresponding acetaldehydhydrazones[7], and *p*-methoxyphenylhydrazone of *tert.*-butyl levulinate (**2**)[9] were prepared according to literature directions. All hydrazones exhibited characteristic IR bands at 3310—3350 (Ar-NH), 1630—1640 (C=N), 1345—1350 cm^{-1} (Ar—N); NMR-spectra of acetaldehyde-hydrazones contained characteristic doublets at 1.88 ppm (—CH_3) and quartets at 6.85 ppm (—CH=N).

1-(p-Chlorophenyl)-5-(p-methoxyphenyl)-3-methylpyrazol (**3**)

The Na-salt of *p*-chlorophenylhydrazine sulfonic acid (5.0 g, 20 mmol) was slurried in 90% ethanol (25 ml), conc. hydrochloric acid (1.6 ml, 20 mmol) was added, and the whole was heated under reflux for 15 min. To the hot solution sodium acetate (2.8 g, 21 mmol) dissolved in water (5 ml) and *p*-methoxybenzoylacetone (3.5 g, 18 mmol) were added. After a brief period of heating under reflux, the reaction mixture was allowed to cool slowly, and upon reaching ambient temperature was poured into ice-cold water (150 ml). The aqueous layer was decanted from the yellow oily product, and the latter was repeatedly washed with water. Crude **3** crystallized slowly on standing in dessicator. Recrystallization from ethanol, with addition of charcoal, gave 3.2 g (60%) of **3**, m. p. 103—105 °C. NMR ($CDCl_3$) 2.35 (s, 3H), 3.75 (s, 3H), 6.23 (s, 1H), 6.97 (dd, 4H), 7.24 (dd, 4H).

Anal. for $C_{17}H_{15}ClN_2O$ (298.76) calc'd.: C 68.34; H 5.06; N 9.38%
found: C 68.17; H 4.87; N 9.09%

1-(p-Chlorophenyl)-5-(p-bromophenyl)-3-methylpyrazol (**4**)

Starting from the Na-salt of *p*-chlorophenylhydrazine sulfonic acid (5.0 g, 20 mmol), a free base was prepared as described for **3**. All attempts to condense it with *p*-bromobenzoylacetone led to cyclization into **4**. Working under the same reaction conditions as described for **3**, compound **4** was isolated in 58% yield, m. p. 133—135 °C (from ethanol). NMR ($CDCl_3$) 2.38 (s, 3H), 6.33 (s, 1H), 6.7—7.3 (m, 8H).

Anal. for $C_{16}H_{12}BrClN_2$ (347.64) calc'd.: C 55.28; H 3.48; N 8.05%
found: C 54.91; H 3.22; N 8.17%

N(1)-(p-Methoxyphenyl)-N(1)-(p-chlorobenzoyl)-N(2)-benzaldehyde hydrazone (**5**)

Benzaldehyde *p*-methoxyphenylhydrazone (0.70 g, 3.0 mmol) was dissolved in a mixture of aqueous sodium hydroxyde (10 ml, 6.0 mmol NaOH) and dioxane (3.0 ml) by gradual addition with ice-cooling and stirring. To the resulting solution p-chlorobenzoylchloride (1.0 g, 6.0 mmol) was added dropwise over a period of 0.5 h. During this period the crude product crystallized and was separated by suction (1.2 g). On recrystallization from benzene-light petroleum (40—60 °C), pure **5** was obtained (0.8 g, 80% yield), m. p. 156—158 °C. NMR ($CDCl_3$) 3.84 (s, 3H), 6.98 (s, 1H), 7.22 (dd, 4H), 7.39 (s, 5H), 7.62 (dd, 4H).

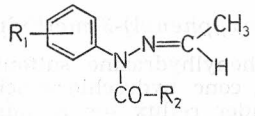
Anal. for $C_{21}H_{17}ClN_2O_2$ (364.82) calc'd.: C 69.14; H 4.70; N 7.68%
found: C 68.92; H 4.87; N 7.50%

General procedure for preparation of N*(1)*-p*-substituted-phenyl*-N*(1)*-*-acyl*-N-*(2)-acetaldehyde hydrazones* **6—11**

p-Substituted phenylhydrazones of acetaldehyde (30 mmol) were dissolved in dry pyridine (20 ml), and the solution was cooled in ice. Substituted benzoylchlorides (38 mmol) were added dropwise with cooling and stirring over a period of 1 h. After an additional 4 h stirring at ambient temperature, the pasty reaction mixture was diluted with ice-water (150 ml). After standing overnight in an ice box, the crude products crystallized, and were collected on a filter by suction. After having been thoroughly washed with water, the solids were dried in a dessicator over conc. sulfuric acid. When the crude products had separated as oils, the aqueous layer was decanted, the oils were washed with water and dried.

All compounds exhibit characteristic IR amide bands at 1660—1670 cm^{-1}, while in NMR spectra no change in the position of the acetaldehydic protons (d, 1.85 ppm, q, 6.8 ppm) was detected. Yields and m. p.'s are given in Table III. These products have been used in the next steps without purification, since they turned out to be highly instable, and decomposed on standing in air or in organic solvents.

TABLE III



Compd. No.	R_1	R_2	m. p./°C	Yield %
6	4-CH_3O-	4-Cl-C_6H_4-	92—95[a]	98
7	4-CH_3O-	3,5-diNO_2-C_6H_4-	oil	100
8	4-CH_3O-	4-CH_3O-C_6H_4-	162—163	98
9	4-CH_3O-	phtalimido-glycyl	162—165 (decc.)	96
10	4-Cl-	4-Cl-C_6H_4-	145—155	75
11	3-Cl-	4-Cl-C_6H_4-	91—93	41

[a] Lit. 7: m. p. 96—100 °C.

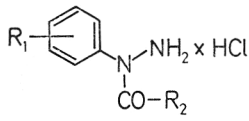
General procedure for preparation of N*(1)-p-substituted-phenyl*-N*(1)*-*-acylhydrazine hydrochlorides* **12—17**

Slurries of crude *N*(1)-*p*-substituted-phenyl-*N*(1)-acyl-*N*(2)-acetaldehyde hydrazones (30 mmol) were preparated with a solvent mixture of toluene (100 ml) and abs. methanol (5.0 ml), and were cooled in an ice-bath with continuous stirring. Dry hydrogen chloride (3—4 g) was bubbled through the mixtures during 1 h. After an additional 15 min stirring at 0 °C, the reaction flask was connected to a water pump and excess hydrogen chloride was removed in vacuo. A crystalline solid separated, and was filtered off with suction, washed with benzene and ether, and dried in vacuo. NMR spectra (CD_3OD) lacked the characteristic signals for a $CH_3CH{=}N{-}$ group, but IR spectra contained characteristic amide bands at 1615—1620 cm^{-1}. Other characteristic constants are presented in Table IV.

General procedure for preparation of N*(1)-acylated-2-methyl-3,5-*-*disubstituted indoles* **18—27**

N(1)-*p*-substituted-phenyl-*N*(1)-acylhydrazine hydrochlorides (10 mmol) and β-dicarbonyl compounds were dissolved in glac. acetic acid (30 ml) and heated at 70—80 °C during 3—6 h. Ammonium chloride separated and was filtered off. Crude

TABLE IV



Compd. No.	R_1	R_2	m. p./°C	Yield %
12	4-CH_3O-	4-Cl-C_6H_4-	164—166[a] (decc.)	83
13	4-CH_3O-	3,5-diNO_2-C_6H_4-	182—104 (decc.)	86
14	4-CH_3O-	4-Cl-C_6H_4-	161—163 (decc.)	89
15	4-CH_3O-	phthalimido-glycyl	145—148 (decc.)	95
16	4-Cl-	4-Cl-C_6H_4-	170—173 (decc.)	85
17	3-Cl-	4-Cl-C_6H_4-	170—172 (decc.)	91

[a] Lit. 7: m. p. 169—172 °C.

compounds **23** and **24** crystallized after chilling the filtrate. In all other instances the solvent was evaporated in vacuo, and traces of acetic acid removed by repeated evaporation with benzene. The remaining crude products were recrystallized from the solvents indicated in Table V.

Compound **21** crystallized in two different forms, one having m. p. 107—109 °C (from light petroleum, pale-yellow crystals), and the other 127—128 °C (from ethyl-acetate-light petroleum, colourless crystals). Their IR spectra in solution ($CHCl_3$), as well as NMR spectra ($CDCl_3$) were identical, while IR spectra of KBr-disks exhibited significant difference in the finger-print region. Attempted thermo-microanalysis of the three mixtures (1 : 3, 1 : 1 and 3 : 1), on the Kofler-microheating stage, failed to give useful results. All mixtures melted at 125—128 °C indicating a transformation of the lower-melting into the higher-melting form while being ground in the mortar.

The polysubstituted indoles listed in Table V exhibited following NMR spectra (solvent, δ):

18 (acetone-d_6) 2.32 (s, 3H), 3.64 (s, 3H), 6.6—7.1 (m, 3H), 7.4—7.9 (m, 9H).

19 ($CDCl_3$) 2.43 (s, 3H), 3.74 (s, 3H), 3.91 (s, 3H), 6.6—7.1 (m, 3H), 7.4—8.0 (m, 8H).

20 (DMF-d_7) 2.36 (s, 9H; 3 × CH_3), 3.73 (s, 3H), 6.7—8.1 (m, 10H).

21 ($CDCl_3$) 2.32 (s, 3H), 3.71 (s, 3H), 3.90 (s, 3H), 6.6—7.2 (m, 5H), 7.5—8.0 (m, 6H).

22 (DMF-d_7) 2.29 (s, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 3.89 (s, 3H), 6.6—8.0 (m, 10H).

23 (acetone-d_6) 2.30 (s, 3H), 3.65 (s, 3H), 6.6—7.1 (m, 3H), 7.4—8.0 (m, 8H).

24 (DMF-d_7) 2.32 (s, 3H), 3.73 (s, 3H), 6.5—7.2 (m, 5H), 7.6—8.1 (m, 6H).

25 (DMF-d_7) 2.35 (s, 3H), 3.68 (s, 3H), 6.7—8.6 (m, 14H).

26 (acetone-d_6) 2.32 (s, 3H), 3.65 (s, 3H), 3.91 (s, 3H), 6.6—7.1 (m, 3H), 7.4—8.0 (m, 8H).

27 (DMF-d_7) 2.38 (s, 3H), 3.67 (s, 3H), 3.96 (s, 3H), 6.7—8.5 (m, 14H).

28 (DMF-d_7) 2.32 (s, 3H), 3.70—3.85 (m, 2H), 3.78 (s, 3H), 3.88 (s, 3H), 6.6—7.8 (m, 8H).

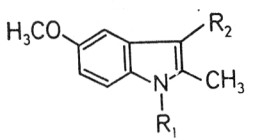
29 (DMF-d_7) 2.32 (s, 3H), 3.7—3.9 (m, 2H), 3.84 (s, 3H), 6.7—7.3 (m, 3H), 9.0—9.3 (m, 3H).

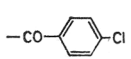
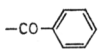
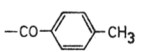
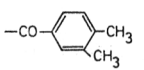
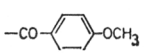
1-p-Chlorobenzoyl-2,3-dimethyl-5-chloroindole (**30**)

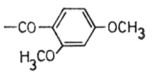
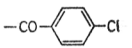
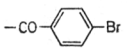
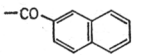
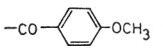
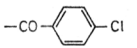
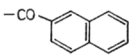
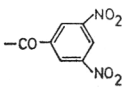
N(1)-*p*-Chlorophenyl-*N*(1)-*p*-chlorobenzoylhydrazine hydrochloride (1.6 g, 5.0 mmol) in 6.0 ml of methyl-ethylketone was heated under reflux for 3 h. Excess ketone was evaporated in vacuo and the residue was crystallized from aqueous acetone. Pure **30**, 1.27 g (80%), yellow crystals had a m. p. 128—130 °C. NMR (DMSO-d_6) 2.20 (s, 6H; 2 × CH_3), 7.1—7.7 (m, 7H).

Anal. for $C_{17}H_{13}Cl_2NO$ (318.18) calc'd.: C 64.16; H 4.11; N 4.40%
found: C 64.03; H 3.90; N 4.16%

TABLE V



Compd. No.	R_1	R_2	Formula	m. p.[a] °C	Yield %	Calc'd./%			Found/%		
						C	H	N	C	H	N
18			$C_{24}H_{18}ClNO_3$	112—114	31	71.37	4.49	3.47	71.23	4.64	3.36
19	—‖—		$C_{25}H_{20}ClNO_3$	142—144	52	71.84	4.83	3.35	71.81	5.16	3.35
20	—‖—		$C_{26}H_{22}ClNO_3$	144—146	33	72.30	5.13	3.25	72.50	5.29	3.48
21	—‖—		$C_{25}H_{20}ClNO_4$	127—128	41	69.20	4.65	3.23	69.60	5.04	3.08

22	—‖—		$C_{26}H_{22}ClNO_5$	110—111	58	67.31	4.78	3.02	67.21	4.95	2.74
23	—‖—		$C_{24}H_{17}Cl_2NO_3$	181—183	62	65.76	3.91	3.19	65.53	4.25	3.05
24	—‖—		$C_{24}H_{17}BrClNO_3$	185—186	53	59.71	3.55	2.90	59.63	3.73	2.95
25	—‖—		$C_{28}H_{20}ClNO_3$	143—145	43	74.08	4.45	3.09	73.79	4.67	3.17
26			$C_{25}H_{20}ClNO_4$	141—143	51	69.20	4.65	3.23	69.50	4.87	3.43
27	—‖—		$C_{29}H_{23}NO_4$	135—137	48	77.49	5.16	3.11	77.42	5.33	3.27
28	—‖—	$-CH_2COOH$	$C_{20}H_{19}NO_5$	163—165[b]	75	67.98	5.42	3.96	67.64	5.53	4.20
29		$-CH_2COOH$	$C_{19}H_{15}N_3O_8$	219—221[c]	70	55.21	3.65	—	55.47	3.41	—

[a] All samples recrystallized from EtOH, except **21** (EtOAc — light petroleum), and **28** (50% aq. EtOH).
[b] M. p. 88—89 °C cited in ref. 19 seems to belong to the ethylester of the acid **28**, [c] No data cited in *Chem. Abstr.* — ref. 20.

1-p-Chlorobenzoyl-2,3-dimethyl-5-methoxyindole (**31**)

Starting from *N*(1)-*p*-methoxyphenyl-*N*(1)-*p*-chlorobenzoylhydrazine hydrochloride (1.6 g, 5.0 mmol) and 6.0 ml of methyl-ethylketone, crude **31** was prepared in the same manner as described for **30**. On recrystallization from 70% ethanol, 1.17 g (75%) of **31** with m. p. 81—83 °C was obtained (lit. 21: m. p. 93—94 °C). NMR (DMSO-d_6) 2.21 (s, 6H; 2 × CH_3), 3.75 (s, 3H), 7.2—7.8 (m, 7H).

Anal. for $C_{18}H_{16}ClNO_2$ (313.77) calc'd.: C 68.90; H 5.14; N 4.46%
found: C 69.11; H 5.33; N 4.28%

1-p-Chlorobenzoyl-2-methyl-3-(2'-methyl-4'-nitroimidazol-1'-yl)-5-methoxyindole (**32**)

N(1)-*p*-Methoxyphenyl-*N*(1)-*p*-chlorobenzoylhydrazine hydrochloride (3.2 g, 10.0 mmol) and 1-(2'-oxopropyl)-2-methyl-4-nitroimidazole[22] (1.8 g, 10.0 mmol) were dissolved in glac. acetic acid (20 ml) and heated at 90—100 °C for 8 h. An inorganic precipitate was filtered off, and the filtrate was chilled on ice, giving 1.83 g (43%) of crystalline **32** which, on recrystallization from aqueous acetone, melted at 224—226 °C. IR (KBr) 1690, 1590, 1540, 1495, 1465, 1255, 1180, 765 cm^{-1}. NMR ($CDCl_3$) 2.21 (s, 6H; 2 × CH_3), 3.92 (s, 3H), 3.99 (s, 3H), 6.62 (q, 1H), 6.8—7.3 (m, 4H), 7.75 (s, 1H), 7.88 (s, 2H).

Anal. for $C_{21}H_{17}ClN_4O_4$ (424.83) calc'd.: C 59.37; H 4.03%
found: C 59.14; H 4.24%

1-p-Methoxybenzoyl-3-methyl-3-(2'-methyl-4'-nitroimidazol-1'-yl)-5-methoxyindole (**33**)

Compound **33** was prepared by starting from *N*(1)-*p*-methoxyphenyl-*N*(1)-*p*-methoxybenzoylhydrazine hydrochloride (2.15 g, 7.0 mmol), using the same reaction conditions as described for **32**. The crude product (1.5 g) was purified by recrystallization from methylene chloride — light petroleum. Yield 1.2 g (40%), m. p. 227—229 °C. IR (KBr) 1700, 1610, 1590, 1540, 1500, 1465, 1310 cm^{-1}. NMR (DMF-d_7) 2.28 (s, 6H; 2 × CH_3), 3.73 (s, 3H), 3.88 (s, 3H), 6.5—7.8 (m, 8H).

Anal. for $C_{22}H_{20}N_4O_5$ (420.41) calc'd.: C 62.85; H 4.79%
found: C 62.91; H 4.84%

N-*Propargyl*-N-*(4'-chlorobenzoyl)-4-methoxyaniline* (**35**)

N-(4'-Chlorobenzoyl)-4-methoxyaniline (m. p. 207—208 °C 12.2 g, 46.6 mmol) was alkylated with propargyl bromide (10.0 g, 84.1 mmol) in DMF (150 ml), in the presence of barium oxyde (10.0 g). After stirring for 24 h at room temperature, cellite (»filter aid«, 2—3 g) was added, and the inorganic precipitate was filtered off. The filtrate was evaporated to dryness at 50 °C in vacuo, the residual oil was emulsified with water (200 ml) and extracted with ether (3 × 100 ml). After drying (Na_2SO_4) ethereal extracts were evaporated, and residual crude **35** was crystallized from diisopropylether, giving 8.46 g (60.5%) of pure substances with m. p. 81—82 °C. NMR ($CDCl_3$) 2.23 (t, 1H), 3.73 (s, 3H), 4.60 (d, 2H), 6.7—7.5 (m, 8H).

Anal. for $C_{17}H_{14}ClN_2O$ (299.76) calcl'd.: C 68.12; H 4.70; N 4.67%
found: C 67.90; H 4.86; N 4.83%

N-*Allyl*-N-*(4'-chlorobenzoyl)-4-methoxyaniline* (**36**)

Starting from *N*-(4'-chlorobenzoyl)-4-methoxyaniline (5.5 g, 21.8 mmol), allyliodide (5.0 g, 30.0 mmol) and barium oxyde (5.0 g) in DMF (80 ml), compound **36** was prepared by using the same manner as described for **35**. After extracting the crude product into ether, drying and evaporation, the residue was distilled at 180—185 °C/0.03 mm Hg, to give pure oily **36** (5.6 g, 85%). This oil crystallized after lengthy standing on ice; m. p. 29—32 °C. NMR ($CDCl_3$) 3.67 (s, 3H), 4.37 (d, 2H), 4.9—5.3 (m, 2H), 5.6—6.1 (m, 1H), 6.6—7.2 (m, 8H).

Anal. for $C_{17}H_{16}ClN_2O$ (301.78) calc'd.: C 67.67; H 5.34; N 4.64%
found: C 67.48; H 5.48; N 4.39%

Cyclization of the compound (**35**)

Compound **35** (2.89 g, 9.66 mmol) was dissolved in sulfolane (50 ml, dried before use by distillation over KOH-pellets, bp 110—112 °C/0.03 mm Hg), and heated at 230 °C by using a Wood's metal bath. The reaction was conducted in an atmosphere of carefully dried nitrogen, and monitored by TLC chloroform-light petroleum (95 : 5) as the eluant. After heating for 18 h, the sulfolane was evaporated at 0.2 mm Hg, the residue was emulsified with 100 ml of water and extracted into ether (3 × 50 ml). The ethereal extracts were washed with brine (3 × 50 ml), dried and evaporated. The resulting mixture was fractionated on a silicagel column (90 g), using chloroform as the eluant; 5-ml fractions were collected. The fractional distribution was as follows 120—125, pure **38** (53 mg); 126—159, unreacted **35** (798 mg); 163—167, *N*-(4'--chlorobenzoyl)-4-methoxyaniline (i. e. dealkylated **35**, 125 mg); 168—176, a mixture of dealkylated **35** and **37** (860 mg); 177—182, pure **37** (388 mg).

1-(4'-Chlorobenzoyl)-2-methyl-5-methoxyindole (**38**)

Compound **38**, obtained from fractions 120—125, exhibited the following signals in the NMR spectrum ($CDCl_3$): 2.38 (s, 3H), 3.80 (s, 3H), 6.35 (s, 1H), 6.5—7.7 (m, 7H). On recrystallization from methanol it melted at 60—63 °C.

An authentic sample of **38** was prepared from 2-methyl-5-methoxyindole (2.3 g, 14.2 mmol, prepared according to ref. 23 but with 35.6% yield, in contrast to 1% claimed by the original authors), which was converted into the Na-salt by dissolving in DMF (80 ml) and gradually adding sodium hydride (1.0 g, 20 mmol, as a 50% suspension in mineral oil). After 0.5 h stirring at ambient temperature, the resulting solution was ice-cooled, and *p*-chlorobenzoylchloride (2.4 ml, 18 mmol) was added dropwise. Stirring at 0 °C was continued for 8 h, then the reaction mixture was poured into 250 ml of water containing 2.5 ml of acetic acid. The product was extracted with ether (3 × 50 ml), then with benzene (2 × 50 ml). The combined extracts were washed with satd. aqueous sodium bicarbonate, dried, evaporated and crude **38** crystallized from methanol giving 3.2 g (76.2%), mp. 63—65 °C.

Anal. for $C_{17}H_{14}ClNO_2$ (299.75) calc'd.: C 68.11; H 4.71; N 4.67%
found: C 67.87; H 4.92; N 4.94%

N-*(2'-Oxopropyl)*-N-*(4'-chlorobenzoyl)-4-methoxyaniline* (**37**)

The product isolated from fractions 177—182 (see above) was recrystallized from diisopropylether, m. p. 96—98 °C. IR (KBr) 3010, 2980, 1730, 1645, 1588, 1510, 1405, 1372, 1243, 1222, 1086, 1010, 842, 836 and 755 cm^{-1}. NMR ($CDCl_3$) 2.33 (s, 3H), 3.77 (s, 3H), 4.63 (s, 2H), 6.6—7.6 (m, 8H).

Anal. for $C_{17}H_{16}ClNO_3$ (317.77) calc'd.: C 64.25; H 5.08; N 4.42%
found: C 64.57; H 5.12; N 4.68%.

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SAŽETAK

Sinteze novih derivata indola sličnih indometacinu

M. Mihalić, V. Šunjić, F. Kajfež, V. Čaplar i T. Kovač

Opisane su priprave i svojstva novih derivata indola **18**—**33**, kao potencijalnih antiinflamatornih sredstava. 1-*p*-Klorbenzoil-2-metil-3-(2'metil-4'-nitroimidazol-1'-il)-5-metoksiindol (**32**) pokazao je izrazito antiinflamatorno djelovanje uz vrlo nisku ulcerogenost. Pokušavajući pripravu *N*-benzoil-indolskog derivata **38** sigmatropnom pregradnjom lančastog prekursora **35**, što je bio modelni postupak za novu sintezu indometacina, redovito su postignuta niska iskorištenja željenoga cikličkog produkta **38**.

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COMPAGNIA DI RICERCA CHIMICA, C R C,
33048 SAN GIOVANNI AL NATISONE (UD), ITALIJA

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