ESTERS OF 1-*p*-CHLOROBENZOYL-5-METHOXY-2-METHYL-3-INDOLYLACETIC ACID

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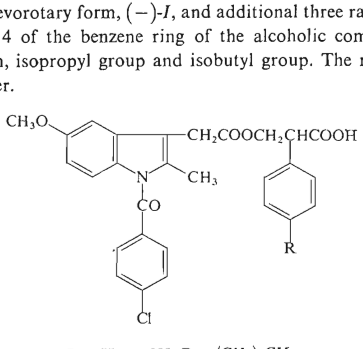
Reactions of imidazolide of 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid, prepared from the acid and N,N'-carbonyldiimidazole, with the optically active forms of 2-phenyl-3-hydroxypropane acid and with the inactive forms of *p*-chloro-, *p*-isopropyl- and *p*-isobutyl-2-phenyl-3-hydroxypropane acids gave the corresponding esters. The compounds were tested for antiinflammatory activity.

Studying the pharmacological properties of esters of 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid (known for its antiinflammatory action as indomethacin), we have recently prepared[1] a series of compounds, of which the (±)-2-phenyl-2-carboxyethyl ester, (±)-*I*, appears to be the most promising. While retaining the efficacy of indomethacin this ester has proved to be much less toxic. The favourable results of biochemical and pharmacological tests with the ester (±)-*I* have led us to studying the differences between the racemic compound and its optical isomers and the effect of substitution on the benzene ring of the alcoholic component of the ester.

We have prepared the two optic isomers of the ester (±)-*I*, the dextrorotary form, (+)-*I*, the laevorotary form, (−)-*I*, and additional three racemic esters, *II* – *IV*, in which position 4 of the benzene ring of the alcoholic component is occupied by a chlorine atom, isopropyl group and isobutyl group. The results are described in the present paper.



I, R = H *III*, R = $(CH_3)_2CH$
II, R = Cl *IV*, R = $(CH_3)_2CHCH_2$
Ia – *IVa* cyclohexylammonium salts

Since our attempts at resolution of the racemic form of the ester (±)-*I* had ended in failure, a chirality centre was introduced into the molecules of the esters (+)-*I*, and (−)-*I* by means of the optically active 2-phenyl-3-hydroxypropane acid. All the esters were prepared by the procedure used with the racemic form of the ester[1]. This consisted in conversion of 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid by N,N′-carbonyldiimidazole[2], in dichloromethane at room temperature, into an imidazolide, which reacted *in situ* with the alcoholic component. As was found by thin-layer chromatography, the crude reaction product contained 20−30% of the unreacted indolylacetic acid, which was difficult to separate by the usual purification methods. The compounds were separated after conversion into cyclohexylammonium salts; under the conditions used the salt of the carboxy ester crystallized from the solvent and the starting indolylacetic acid remained in the solution. Since the optically active carboxy esters readily form hydrates they were released from their salts by gaseous hydrogen chloride in a water-free medium. The salts of the other carboxy esters were decomposed by hydrochloric acid. After this operation the content of the starting indolylacetic acid in the carboxy esters was reduced to a trace amount.

The optically active forms of 2-phenyl-3-hydroxypropane acid were obtained from the racemic acid by resolution with threo-D(−) and L(+)-1-*p*-nitrophenyl-2-amino-1,3-propanediol[3]. The substituted 2-phenyl-3-hydroxypropane acids were prepared by hydrolysis of their esters, using the procedure for preparation of 2-phenyl-3-hydroxypropane acid[4]. The esters were obtained by hydroxymethylation of the phenyl acetates according to the procedure described for synthesis of *p*-methoxy-2-phenyl-3-hydroxypropane acid[5].

In pharmacological tests of the optical isomers the dextrorotary one, (+)-*I* was about 50% less toxic and in the test for kaolin oedema[6] it effected in a lower dose about 100% stronger inhibition of the oedema than the laevorotary and the racemic forms did. No difference was found between the laevorotary and the racemic forms both in toxicity and efficacy. The derivatives *II*−*IV* had the efficacy of the non-substituted ester (±)-*I*, but were by 40−100% more toxic; the relatively least toxic was the isopropyl derivative *III*, the maximum toxicity was observed with the isobutyl derivative *IV*.

EXPERIMENTAL

The uncorrected melting points were determined on the Kofler block. Ascending thin-layer chromatography was carried out on commercial silica gel plates Fertigplatten Kieselgel 60 F_{254} Merck in a saturated separation chamber (2 h) in the system chloroform–methanol–acetic acid–water (85 : 5 : 5 : 2); the path length was 15 cm. Ten μl of 1% solutions of the samples in chloroform (100 μg) was applied. The spots on the chromatogram were detected by fluorescence quenching at 254 nm. The amount of free 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic

acid was determined semiquantitatively by visual assessment of the quenching compared with a calibration series of standards. The optical rotation was determined with a polarimeter Perkin–Elmer 141.

TABLE I

Carboxy Esters and Their Cyclohexylammonium Salts

Compound[a,b] (yield, %)[c]	M.p., °C (solvent)[d]	R_F[e] $[\alpha]_D^{20}$ [f]	Formula (m.w.)	Calculated/Found			
				% C	% H	% N	% Cl
(+)-*I*	72—73	0·72	$C_{28}H_{24}ClNO_6$	66·47	4·78	2·77	7·00
62	(ethanol)	28·7	(505·9)	66·47	4·99	2·88	6·95
(+)-*Ia*	153—155	0·72[g]	$C_{34}H_{37}ClN_2O_6$	67·48	6·16	4·63	5·86
81	[d]	28·4	(605·1)	67·42	6·20	4·74	5·71
(—)-*I*	72—73	0·72	$C_{28}H_{24}ClNO_6$	66·47	4·78	2·77	7·00
61	(ethanol)	28·6	(505·9)	66·30	4·90	2·80	7·04
(—)-*Ia*	153—155	0·72[g]	$C_{34}H_{37}ClN_2O_6$	67·48	6·16	4·63	5·86
80	[d]	28·2	(605·1)	67·42	6·04	4·56	6·00
II	129—130	0·69	$C_{28}H_{23}Cl_2NO_6$	62·23	4·29	2·59	13·12
43	(nitromethane)	—	(540·4)	62·18	4·30	2·54	13·26
IIa	154—156	0·69[g]	$C_{34}H_{36}Cl_2N_2O_6$	63·85	5·67	4·38	11·09
65	[d]	—	(639·6)	63·63	5·58	4·20	11·22
III	139—140	0·75	$C_{31}H_{30}ClNO_6$	67·94	5·52	2·56	6·47
55	(nitromethane)	—	(548·0)	67·84	5·54	2·46	6·50
IIIa	152—154	0·75[g]	$C_{37}H_{43}ClN_2O_6$	68·66	6·69	4·33	5·47
80	[d]	—	(647·2)	68·53	6·64	4·34	5·50
IV	87—89	0·75	$C_{32}H_{32}ClNO_6$	68·38	5·74	2·49	6·30
57	(ethanol–water)	—	(562·1)	68·56	5·79	2·45	6·16
IVa	140—142	0·75[g]	$C_{38}H_{45}ClN_2O_6$	69·03	6·86	4·24	5·36
73	[d]	—	(661·2)	68·83	7·05	4·11	5·44

[a] Reported[1] m.p. of the racemic ester (±)-*I* is 132—133°C. [b] Cyclohexylammonium salt of the racemic ester (±)-*Ia*: m.p. 153—154°C (methanol–diisopropyl ether); for $C_{34}H_{37}ClN_2O_6$ (605·1) calculated: 67·48% C, 6·16% H, 4·63% N, 5·86% Cl; found: 67·33% C, 6·30% H, 4·73% N, 6·10% Cl. [c] In calculating the yields of the esters 20% of the starting acid was supposed to have been recovered; with the cyclohexylammonium salts the yields are based on the determined contents of the carboxy esters. [d] Methanol–diisopropyl ether. [e] R_F of 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid is 0·64. [f] $c = 2$, ethanol. [g] Chromatography of the cyclohexylammonium salts occasioned their dissociation. The main spot had the mobility of the corresponding carboxy ester.

(+) and (—)-2-Phenyl-2-carboxyethyl Esters
of 1-*p*-Chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic Acid ((+)-I and (—)-I)

To a stirred solution of 97% N,N'-carbonyldiimidazole (6·68 g, 0·04 mol) in dichloromethane (80 ml) was added under nitrogen 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid (14·32 g, 0·04 mol) at room temperature. After 5 min the imidazolide thus prepared was treated with (+)-2-phenyl-3-hydroxypropane acid[3] (6·64 g, 0·04 mol). The mixture was stirred for 3 more hours and left standing for 16 h at room temperature. It was washed with dilute hydrochloric acid, then with water until its pH was neutral. The dichloromethane solution was dried with magnesium sulphate and concentrated under reduced pressure; yield 18·6 g of the crude product, containing about 30% of the starting indolylacetic acid. The same procedure starting from (—)-2-phenyl-3-hydroxypropane acid gave 18·3 g of the crude laevorotary isomer. For analysis a sample of the imidazolide was isolated; m.p. 130—132°C (toluene). For $C_{22}H_{18}ClN_3O_3$ (407·8) calculated: 64·79% C, 4·45% H, 10·30% N, 8·69% Cl; found: 64·91% C, 4·75% H, 10·10% N, 8·48% Cl.

Cyclohexylammonium Salts of the Carboxy Esters (+)-Ia and (—)-Ia

To the crude, *c.* 70% dextrorotary carboxy ester (18·6 g, *c.* 0·026 mol) in acetone (186 ml) was added cyclohexylamine (2·6 g, 0·026 mol) in acetone (35 ml) and the mixture was left standing for 3 h at room temperature. Crystals (12·65 g) of the cyclohexylammonium salt of the dextrorotary isomer (containing 0·5—1% of the starting indolylacetic acid) separated from the solution. In this form the salt was decomposed. The salt of the carboxy ester was filtered off and 1·6 g of cyclohexylamine was added to the mother liquor; yield 5·3 g of the cyclohexylammonium salt of 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid[7]. Decomposition, described with the carboxy esters *II*—*IV*, and crystallization from nitromethane gave 3 g of the pure acid. Following the same procedure 18·3 g of the crude laevorotary isomer gave 12·4 g of the carboxy ester cyclohexylammonium salt and 5·15 g of the salt of the starting acid.

Decomposition: To a suspension of the dextrorotary carboxy ester cyclohexylammonium salt (12·2 g, 0·02 mol) in ether (400 ml) was added ether saturated with gaseous hydrogen chloride (7·2 ml, containing 0·2 g in 1 ml, 0·04 mol) and the mixture was stirred for 10 min in the absence of air. Cyclohexylamine hydrochloride was filtered off in a nitrogen atmosphere and the filtrate was distilled under reduced pressure to remove the ether. The dry residue (10·65 g) was crystallized from ethanol; yield 9·6 g of the dextrorotary carboxy ester. Using the same procedure 12·0 g of the laevorotary carboxy ester cyclohexylammonium salt gave 10·4 g of the dry residue and 9·4 g of the pure laevorotary carboxy ester. Analytical samples of the optically active esters were dried 24 h at 50°C/13·3 Pa. The melting points of the optically active isomers are lower than that of the racemic form. This value was reached with a mixture of equal parts of the two isomers after crystallization from nitromethane.

Carboxy Esters *II-IV*

The crude carboxy esters were obtained by the procedure described for the optically active isomers from 0·01 mol of 1-*p*-chlorobenzoyl-5-methoxy-3-indolylacetic acid, 0·01 mol of N,N'-carbonyldiimidazole and 0·01 mol of *p*-chloro-, *p*-isopropyl- and *p*-isobutylphenyl-3-hydroxypropane acids. The content of the starting indolylacetic acid in the crude carboxy esters *II* and *III* was 20 to 30%, in *IV* it was 15—20%. Cyclohexylamine was taken in a quantity corresponding to the minimum content of the ester determined by chromatography. Cyclohexylammonium salts of the three carboxy esters were decomposed as the crude products by an excessive portion

of *c.* 20% aqueous hydrochloric acid in the presence of ether. The ethereal solutions were washed with water, dried with magnesium sulphate, ether was distilled off *in vacuo* and the dry residues were crystallized. The mother liquors were treated with more cyclohexylamine and decomposed with hydrochloric acid. About 20% of the starting indolylacetic acid was recovered in all cases.

Substituted 2-Phenyl-3-hydroxypropane Acids

Hydroxymethylation of phenyl acetates: A mixture of 0·1 mol of ethyl *p*-chlorophenyl acetate (*p*-isopropyl, *p*-isobutylphenyl acetate), 3 g of paraformaldehyde, 10 ml of 0·5M sodium ethylate in ethanol and 100 ml of dimethyl sulphoxide was stirred for 30 min at room temperature. After neutralization with acetic acid and removal of dimethyl sulphoxide *in vacuo* the crude *p*-chloro- and *p*-isopropyl derivatives were purified by distillation; ethyl ester of *p*-isobutyl--2-phenyl-3-hydroxypropane acid was hydrolysed in the crude state. Ethyl ester of *p*-chloro--2-phenyl-3-hydroxypropane acid was obtained in a 50% yield, b.p. 125—128°3/53·2 Pa. For $C_{11}H_{13}ClO_3$ (228·7) calculated: 57·77% C, 5·73% H, 15·50% Cl; found: 57·83% C, 5·68% H, 15·45% Cl. The yield of ethyl ester of *p*-isopropyl-2-phenyl-3-hydroxypropane acid was 68%; b.p. 131—132°C/53·2 Pa. For $C_{14}H_{20}O_3$ (236·3) calculated: 71·16% C, 8·53% H; found: 71·02% C, 8·48% H.

Hydrolysis of the ethyl esters: Ethyl ester of *p*-chloro-2-phenyl-3-hydroxypropane acid (*p*-isopropyl-, *p*-isobutyl-2-phenyl-3-hydroxypropane acid) (0·05 mol) was refluxed with an ethanolic solution of sodium hydroxide (prepared from 1·17 g of sodium, 35 ml of ethanol and 1·5 ml of water) for 5 min and the mixture was left standing for 3 h at room temperature. The separated salt of the acid was dissolved in a minimum of water, the acid was released with hydrochloric acid and extracted into ether. The ethereal solution was dried with magnesium sulphate, distilled to remove the ether and the dry residue, 2·9 g (7·25 g and 8·34 g) was crystallized. *p*-Chloro--2-phenyl-3-hydroxypropane acid, 2·5 g (12·5%), m.p. 140—142°C (toluene); for $C_9H_9ClO_3$ (200·6) calculated: 53·88% C, 4·52% H, 17·67% Cl; found: 53·98% C, 4·52% H, 17·56% Cl. *p*-Isopropyl-2-phenyl-3-hydroxypropane acid, 6·3 g (30%), m.p. 99—100°C (cyclohexane); for $C_{12}H_{16}O_3$ (208·3) calculated: 69·21% C, 7·74% H; found: 68·98% C, 7·90% H. *p*-Isobutyl--2-phenyl-3-hydroxypropane acid, 8·34 g (38%), m.p. 101—103°C (cyclohexane); for $C_{13}H_{18}O_3$ (222·3) calculated: 70·24% C, 8·16% H; found: 70·34% C, 8·19% H.

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