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SYNTHESIS OF NEW OPTICALLY ACTIVE α-ALKOXYPROPIONANILIDES

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Abstract—Two promising routes towards synthesis of the hitherto unknown α-alkoxypropionanilides were explored with success. As expected, facile displacement of the bromide in L(−)α-bromopropionanilide by alkoxide lead to inversion of configuration with considerable racemization, whereas substitution of the chloride in L(−)α-alkoxypropionyl chloride by arylamine proceeded with little or no racemization. α-Ethoxypropionanilide and the higher alkoxy homologues appear as low-melting non-crystallizable gum. Optical properties and other physical data for few model compounds of this new anilide series are reported.

Optically active α-alkoxypropionanilides are O-alkyl derivatives of lactic acid and could be useful potential drugs. We have recently prepared a series of optically active α-halopropionanilides[1] and investigated their chiroptical properties through CD-technique.[2] Similar CD studies on α-alkoxypropionanilides are desirable for conformational analysis and configurational assignments. Such studies may also provide more information on the applicability of the modified rules[3] for the aromatic chromophore. These objectives, prompted us to undertake the synthesis of these hitherto unknown α-alkoxypropionanilides and this forms the basis of the present work.

For synthesis of α-alkoxypropionanilides, the following two routes were employed:

(1) *Reaction of α-alkoxypropionyl chlorides with arylamines.* L(−)α-alkoxy esters were prepared from L(−)ethyl lactate by reaction with alkyl iodide and silver oxide, following known procedure.[4,5] Saponification of these esters (10% aqueous NaOH) yielded the corresponding L(−)α-alkoxy acids,[4,5] (Table 1) which were then converted into the respective L(−)α-alkoxypropionyl chlorides[6,7] by reaction with specially purified thionyl chloride[8] under mild and anhydrous conditions. The interaction of crude L(−)α-alkoxypropionyl chloride (IR, $\nu_{C=O}$, 1830 cm^{-1}) with the appropriate arylamine, in anhydrous benzene below 45°, afforded the requisite L(−)α-alkoxypropionanilides (Scheme 1), with little or no racemization. This is evidenced from optical purity determinations,[9] using D(+)α-phenylethylamine as NMR solvent following Pirkle's[10] method.

(2) *Action of sodium alkoxides on α-bromopropionanilides.* The room temperature interaction of methanolic sodium methoxide with DL-α-bromopropionanilide[1] gave DL-α-methoxypropionailide in high yield. Employment of L(−)α-bromopropionanilide,[13] afforded D(+)α-methoxypropionanilide (Scheme 2). Here, inversion of configuration is accompanied by considerable racemization, (*cf* Table 2).

Under similar conditions, sodium bromide was isolated almost quantitatively from the reaction of DL-α-bromopropionanilide[13] with ethanolic sodium ethoxide, propanolic sodium propoxide and buta-

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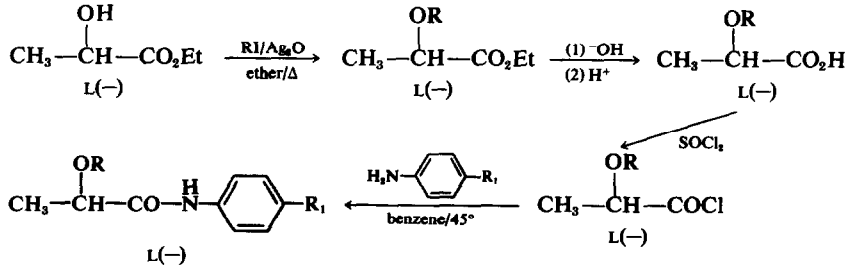


1: R=Me, R_1=H
2: R=Me, R_1=NO_2
3: R=Et, R_1=NO_2

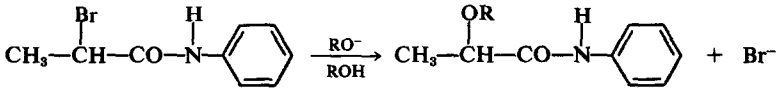
SCHEME 1

Table 1. Physical constants of L(−) α-alkoxy acids and esters

L(−) CH_3—CH(OR)—C(=O)—OR_1

R	R_1	Yield %	b.p.* (C/mm.)	d_4^{20}*	n_D^{20}*	$[\Phi]_D^{20}$*
Me	Et	70	51/20 (46/12)[4]	0·9618 (0·9551)[4]	1·3970	−116·37° (−118·91°)[4]
Et	Et	68	55/20 (58·5–60/16–19)[4]	0·9385 (0·9355)[4]	1·4000 (1·3976)[12]	−108·10° (−116·35°)
n-Pr	Et	63	70/30 (54·8–55·2/11)[11]	0·9188 (0·9194)[11]	1·4069	−100·90°
Me	H	76	99/20 (108–110/30)[4]	1·0928 (1·0908)[4]	1·4122 (1·4131)[7]	−78·46° (−78·49°)[4]
Et	H	71	106/20 (105–6/16–19)[4]	1·0402 (1·0392)[4]	1·4130	−69·58° (−78·30°)[4]
n-Pr	H	65	104/10 (55·5/32·5)[12]	0·9308 (0·9300)[12]	1·4213 (1·3921)[12]	−71·92°

*Lit. data in parentheses.



L(−) D(+)

1*: R=Me

SCHEME 2

nolic sodium butoxide. The products isolated in these cases were, however, gummy oils which could not, as yet, be forced to crystallize.

p-Nitroaniline was the only solid product isolated in high yield from the room temperature reaction of DL-*p*-nitro-α-bromopropionanilide[14] with either MeO^- or EtO^- (15 hr); this implies cleavage of the amide linkage which is promoted, in this case, by the electron withdrawing effect of the nitro group.

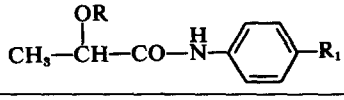
Optical activity. α-Alkoxy esters exhibit somewhat larger molecular rotation than the corresponding acids (*cf* Table 1). The molecular rotation decreases on ascending the series i.e. contribution to molecular rotation by α-alkoxy groups decreases in the following order:

—OMe > —OEt > —OPr

The molecular rotation of α-alkoxyanilides (*cf* Table 2) increase with increased polarity of the solvent, as the following order indicates:

Cyclohexane < Chloroform < Ethanol

Table 2. Analysis and physical constants of α-alkoxypropionanilides



Compound No.	R	R_1	m.p. (Solvent)[a]	Yield %	Analysis %	C	H	N	n_D^{20}	Solvent (c, 1)
1	CH_3	H	45–6°	43	Calc. for $C_{10}H_{13}NO_2$	67·0	7·3	7·8	−89·1°	$CHCl_3$
L(−)			(Pet)		Found	66·8	7·3	7·8	−125·1°	EtOH
									−86·4°	Cyclohexane
2	CH_3	NO_2	110°	52	Calc. for $C_{10}H_{12}N_2O_4$	53·6	5·4	12·5	−95·3°	$CHCl_3$
L(−)			(C_6H_6/Pet)		Found	53·4	5·4	12·7	−155·8°	EtOH
3	C_2H_5	NO_2	72–3°	55	Calc. for $C_{11}H_{14}N_2O_4$	55·5	5·9	11·8	−77·7°	$CHCl_3$
L(−)			(C_6H_6/Pet)		Found	54·9	6·0	11·6	−129·4°	EtOH
1*	CH_3	H	46°	71					+9·3°	$CHCl_3$
D(+)										

[a]Pet = petroleum ether (b.p. 60–80°).

*Synthesized following Scheme (2), M.W. 179 (mass spectrometry).

Substitution of the α-OMe group in compound 2 by an OEt group (3) causes a fall in specific and molecular rotations.

The action of sodium alkylate on optically active α-halopropionic esters was reported[15] to lead to racemic α-alkoxypropionic acids. α-Alkoxyanilides, obtained under similar conditions (Scheme 2) still possess low optical activity. Thus, the molecular rotation exhibited by D(+)α-methoxypropionanilide (compound 1*) is only about 10% of that observed for the L(−) isomer (compound 1, Scheme 1), (*cf* Table 2).

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Optical rotation measurements were taken with the Perkin–Elmer 141 Polarimeter in a cell of 1 cm path length for pure liquids, and a cell of 10 cm path length for the anilides.

L(−)Ethyl α-methoxy-; α-ethoxy and α-propoxy propionates as well as the respective acids have been prepared according to Lit. procedure.[4,5] The physical data of these compounds are listed in Table 1. The respective acid chlorides were synthesized by reaction of the acids with specially purified[8] thionyl chloride, following Lit. procedure;[6,7] these were employed for synthesis of the respective anilides without further purification.

α-Alkoxypropionanilides

General procedure. (a) The acid chloride (0·03 mole) was treated at 0° with a soln of the arylamine (0·03 mole) in anhyd benzene (100 ml). The mixture was stirred at 0–10° for 4 hr, and then for 12 hr at 35–45°, with careful exclusion of moisture. Benzene was evaporated and the residue recrystallized from the appropriate solvent (*cf* Table 2).

(b) The N-aryl α-bromopropionanilide was added to a soln of sodium alkoxide (from 1·5 g Na, 0·065 g atom) in abs alkanol (100 ml). The mixture was stirred for 15 hr at room temp, diluted with water (600 ml) and extracted with ether. The latter solvent was distilled off, and the residue recrystallized from an appropriate solvent.

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