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SYNTHESIS OF SOME 4-(HETARYL)METHYL-γ-LACTONES

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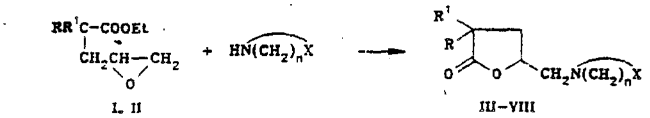
The reaction of alkylglycidylmalonate and alkylglycidylacetoacetate esters with pyrrolidine, piperidine, and morpholine has given butanolides in which these heterocycles are attached to the 4-position of the lactone ring.

Continuing work on the synthesis of functionally-substituted lactones, we have now developed a method for the synthesis of novel butanolides bearing a saturated nitrogen heterocycle at the 4-position of the lactone ring. Accessible starting materials for compounds of this type are alkylglycidylmalonate (I) and alkylglycidylacetoacetate esters (II) [1-4].

Reaction of the oxides (I) with pyrrolidine and piperidine with equimolar amounts of the reactants proceeds with fission of the α-carbon–oxygen bond of the oxide to give the 2-alkyl-2-ethoxycarbonyl-4-pyrrolidinomethyl-4-butanolides (III) or the 2-alkyl-2-ethoxycarbonyl-4-piperidinomethyl-4-butanolides (IV) (Table 1).

Analogously, the interaction of oxides II with pyrrolidine and piperidine leads to the formation of 2-alkyl-4-pyrrolidinomethyl-4-butanolides (V) and 2-alkyl-4-piperidinomethyl-4-butanolides (VI) (Table 1). High yields of the latter are obtained when the oxide–amine ratio is 1:2.

Condensation of the oxides (I) and (II) with morpholine was examined with various ratios of starting materials, to give the 2-alkyl-4-morpholinomethyl-2-ethoxycarbonyl-4-butanolides (VII) and 2-alkyl-4-morpholinomethyl-4-butanolides (VIII) (Table 1).



$R = C_4H_9$, C_5H_{11}, C_6H_{13}; I, III, V, VII $R' = COOEt$; II $R' = COCH_3$; IV, VI, VII $R' = H$;
III, V $n = 3$, IV, VI $n = 4$; $X = CH_2$; VII, VIII $n = 4$, $X = O$

Butanolides (V), (VI), and (VIII) were also obtained by alkaline hydrolysis of butanolides (III), (IV), and (VII).

The addition of heterocyclic amines to oxides (I) and (II) follows Krasuskii's rule, to give the above butanolides.

The hydrochlorides of butanolides (III-VIII) display moderate hypotensive and antiallergic activity. Reduction of the arterial pressure in animals requires near-toxic doses of the hydrochloride of butanolide (IIIa). The hydrochloride of (IVa) has a moderate antidepressant effect.

EXPERIMENTAL

IR spectra were obtained on IKS-14 and IKS-22 spectrometers, in thin films or in vaseline oil. PMR spectra were obtained on Varian T-60 (60 MHz) and Hitachi-Perkin-Elmer R-208 (60 MHz) spectrometers, internal standard tetramethylsilane.

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TABLE 1. Properties of (III)-(VIII)

Compound	mp, °C	bp, °C (0.5 mm)	d_4^{20}	n_D^{20}	Found, %			Empirical formula	Calculated, %			Hydrochloride, mp. °C	Yield, %
					C	H	N		C	H	N		
IIIa		150—153	1,0533	1,4770	64,3	9,0	5,0	$C_{16}H_{17}NO_4$	64,6	9,1	4,7	143	63
IIIb		165—168	1,0443	1,4715	65,3	9,5	4,7	$C_{17}H_{29}NO_4$	65,6	9,3	4,5	110	61
IIIc		185—188	1,0325	1,4708	66,4	9,3	4,4	$C_{18}H_{31}NO_4$	66,5	9,5	4,3	165—166	59
IVa		152—153	1,0495	1,4730	65,2	9,3	4,3	$C_{17}H_{29}NO_4$	65,6	9,3	4,5	—	67
IVb		174—177*	1,0405	1,4755	66,3	9,8	4,5	$C_{18}H_{31}NO_4$	66,5	9,5	4,3	—	60
IVc		165—170	1,0245	1,4725	67,0	9,5	4,1	$C_{19}H_{33}NO_4$	67,3	9,7	4,1	—	58
VIIa		176—178	1,0980	1,4760	61,4	8,8	4,6	$C_{16}H_{27}NO_5$	61,3	8,6	4,5	200—201	81
VIIb		181—182	1,0826	1,4782	62,5	8,7	4,1	$C_{17}H_{29}NO_5$	62,4	8,9	4,3	—	70
VIIc		183—184	1,0730	1,4798	63,3	9,1	4,3	$C_{18}H_{31}NO_5$	63,1	9,3	4,1	199—200	60
Va	51	134—136	—	—	69,4	10,0	6,0	$C_{13}H_{23}NO_2$	69,3	10,2	6,2	185	67
Vb	56	136—139	—	—	70,0	10,4	6,1	$C_{14}H_{25}NO_2$	70,3	10,5	5,9	—	69
Vc	58	155—157	—	—	71,3	10,5	5,9	$C_{15}H_{27}NO_2$	71,2	10,7	5,5	200—201	78
VIa	—	153—156	0,9900	1,4763	69,9	10,4	6,0	$C_{14}H_{25}NO_2$	70,3	10,5	5,9	—	79
VIb	—	158—162	0,9652	1,4754	70,9	10,5	5,3	$C_{15}H_{27}NO_2$	71,2	10,7	5,5	—	60
VIc	—	160—165	0,9699	1,4745	72,1	11,0	5,3	$C_{16}H_{29}NO_2$	71,9	10,9	5,2	—	57
VIIIa	60	170—172	—	—	65,0	9,3	5,7	$C_{13}H_{23}NO_3$	64,7	9,5	5,8	150	73
VIIIb	64	172—174	—	—	65,8	9,7	5,3	$C_{14}H_{25}NO_3$	65,9	9,8	5,5	142	71
VIIIc	67	175—177	—	—	66,5	10,2	5,4	$C_{15}H_{27}NO_3$	66,8	10,1	5,2	138—140	68

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*174-177°C (1 mm).

The alkylglycidylmalonate and alkylglycidylacetoacetate esters (I) and (II) have been obtained previously [1-4].

2-Alkyl-4-pyrrolidino(piperidino or morpholino)methyl-2-ethoxycarbonyl-4-butanolides (III, IV, VII). An equimolar mixture of the oxide (I) and pyrrolidine (or piperidine) was heated in an oil bath for 10 h at 95°C (the mixture of oxide (I) with morpholine was heated for 14 h at 140°C). The mixture was then distilled in vacuo.

The constants of butanolides (III), (IV), and (VII) are given in Table 1.

IR spectra of butanolides (III), (IV), (VII): 1760-1770 (lactone C=O), 1730 cm^{-1} (ester C=O). PMR spectrum (CCl_4): 1.2 (3H, t, J = 7 Hz, $COOCH_2\underline{CH_3}$), 1.65 (4H, m, ring CH_2), 1.9-2.1 (2H, m, 3-CH_2), 2.55 (6H, q, N—CH_2), 3.5 (4H, t, CH_2O in butanolide VII), 4.1 (2H, q, J = 7 Hz, $COO\underline{CH_2}CH_3$), 4.5 ppm (H, m, 4-CH).

2-Alkyl-4-pyrrolidino(piperidino or morpholino)methyl-4-butanolides (V, VI, VIII). A. A mixture of 0.03 mole of the oxide (II) and 0.06 mole of pyrrolidine (or piperidine) was heated in an oil bath for 8 h at 100°C, and the mixture of (II) and morpholine, for 14 h at 120°C. The mixture was then distilled in vacuo (Table 1). IR spectra of butanolides (V), (VI), and (VIII): 1770 cm^{-1} (lactone C=O). PMR spectra (CCl_4): 0.85 (3H, t, CH_3), 1.63 (4H, m, ring CH_2), 2.1 (2H, m, 3-CH_2), 2.55 (6H, q, NCH_2), 3.5 (4H, t, CH_2O in butanolide (VIII)), 4.5 ppm (H, m, 4-CH).

B. A mixture of 0.04 mole of the butanolide (IIIa) or (IVa) and 0.12 mole of 50% sodium hydroxide solution was boiled for 6 h, and the resulting mixture dissolved in water and extracted with ether. The aqueous layer was acidified until neutral to Congo Red, and evaporated on the water bath. The residue was dissolved in absolute alcohol, filtered, the alcohol removed, and the residue distilled in vacuo to give 6.0 g (67%) of (Va), mp 50-51°C (hexane) [6.6 g (69%) of (VIa), bp 152-154°C (0.5 mm), n_D^{20} 1.4763; d_4^{20} 0.9800]. Butanolides (V) and (VI) were readily soluble in alcohol, chloroform, ether, benzene, and acetone, but insoluble in water.

Similarly, from 0.02 mole of the butanolide (VII) and 0.06 mole of 50% sodium hydroxide there was obtained 3.2 g (66%) of the butanolide (VIIIa), mp 60°C (hexane).

The physicochemical data of the butanolides obtained were in agreement with those obtained by method A.

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