REACTION OF ALKYL- AND BENZYLGLYCIDYLMALONIC ESTERS WITH α LACTAMS

É. G. Mesropyan, Yu. A. Bunyatyan,
R. K. Aliev, and M. T. Dangyan

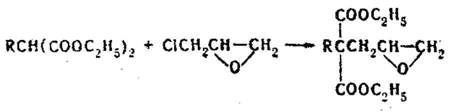
UDC 547.461.8 + 547.745

The reaction of alkyl- and benzylglycidylmalonic esters with pyrrolidinone, piperidinone, and caprolactam in the presence of catalytic amounts of water leads to compounds containing lactone and lactam rings and also to 2-alkyl- and 2-benzyl-5-hydroxy-γ-valerolactones.

It is known [1] that in the reaction of compounds containing oxirane rings with lactams, the oxirane rings are cleaved with the formation of N-substituted lactams having a secondary alcohol group in an open chain.

Continuing a study of the properties of alkylglycidylmalonic esters [2] in order to investigate compounds containing a lactone and a lactam ring, we have performed the condensation of α- lactams with alkyl- and benzylglycidylmalonic esters.

The initial alkyl- and benzylglycidylmalonic esters (Table 1) were synthesized by a known method [2] from alkyl- and benzylmalonic esters and epichlorohydrin:



I–IV

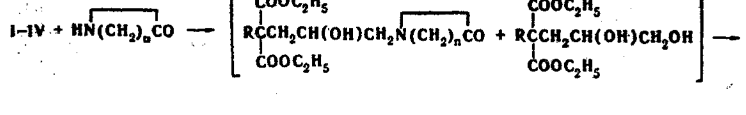
I $R = C_3H_7$; II $R = C_9H_{19}$; III $R = C_{10}H_{21}$; IV $R = C_6H_5CH_2$

The IR spectra of (I-IV) (Table 1) have the bands of the stretching vibrations of C—O, CH in the CH_2 of an epoxide group, and C=O bonds.

Under the action of lactams, the oxirane rings of the alkyl- and benzylglycidylmalonic esters are readily opened in accordance with Krasuskii's rule to form intermediate compounds in which the lactam rings are bound by the nitrogen atom with the γ-carbon atom of β-hydroxyalkylmalonic ester; these compounds readily cyclize even under the conditions of the experiment into γ lactones with the splitting out of an alcohol. Compounds (V-XVI) containing lactone and lactam rings are obtained (Table 2).

The structure of compounds (V-XVI) was confirmed by the IR spectra (Table 2) which lacked the absorption bands of epoxy groups and showed frequencies characteristic for lactone carbonyls and ester and lactam groups.

In the reaction of (I-IV) with lactams, in addition to compounds (V-XVI) certain amounts of the known [3] 2-alkyl- and 2-benzyl-5-hydroxy-γ-valerolactones (XVII-XX) (Table 3) were isolated from the reaction mixtures.



Erevan State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 22-28, January, 1974. Original article submitted October 19, 1972.

TABLE 1. Alkyl- and Benzylglycidylmalonic Esters

Compound	R	bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %		Calculated, %		IR spectra,* ν max, cm^{-1}			Yield, %
					found	calculated		C	H	C	H	C−O	C=O	CH	
I	C_8H_{17}	134—138 (0,5)	0,9875	1,4470	88,75	88,07	$C_{18}H_{32}O_5$	65,6	10,1	65,8	9,7	860	1725	3046	55
II	C_9H_{19}	177—180 (3)	0,9867	1,4490	92,95	92,69	$C_{19}H_{34}O_5$	66,7	10,1	66,6	9,9	860	1730	3046	43
III	$C_{10}H_{21}$	148—152 (1)	0,9830	1,4503	97,53	97,31	$C_{20}H_{36}O_5$	67,6	10,3	67,4	10,1	860	1732	3046	50
IV	$C_6H_5CH_2$	162—163 (4)	1,1352	1,5045	79,85	79.85	$C_{17}H_{22}O_5$	66,5	6,8	66,6	7,2	860	1730	3046	53

---

*Spectra recorded on a IKS-14 instrument in a thin layer.

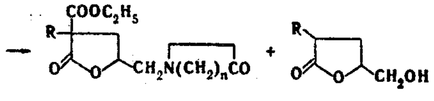
TABLE 2. 2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactones, 2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-4-(2-oxopiperidinomethyl)-γ-butyrolactones, and 2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-5-(2-oxoazepin-1-yl)-γ-valerolactones

Compound	R	n	bp, °C (pressure, mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			IR spectra, ν max, cm^{-1}			Yield, %
						C	H	N	C	H	N	C=O of a lactone	C=O of an ester	C=O of a lactam	
V	C_8H_{17}	3	213—215 (1)	1,4860	$C_{20}H_{33}NO_5$	65,2	8,3	4,1	65,3	8,9	3,8	1775	1730	1692	30
VI	C_9H_{19}	3	198—201 (1)	1,4870	$C_{21}H_{35}NO_5$	66,1	9,6	3,5	66,1	9,2	3,6	1770	1732	1686	51
VII	$C_{10}H_{21}$	3	225—226 (1)	1,4850	$C_{22}H_{37}NO_5$	66,4	9,8	3,9	66,8	9,3	3,5	1772	1730	1693	19
VIII	$C_6H_5CH_2$	3	230—235 (1)	1,5400†	$C_{18}H_{21}NO_5$	65,9	6,6	4,3	65,2	6,3	4,2	1765	1730	1685	21
IX	C_8H_{17}	4	233—234 (1)	1,4910	$C_{21}H_{35}NO_5$	66,5	9,5	3,2	66,1	9,2	3,6	1775	1732	1678	31
X	C_9H_{19}	4	211—214 (1)	1,4935	$C_{22}H_{37}NO_5$	66,4	9,9	3,8	66,8	9,3	3,5	1770	1738	1680	33
XI	$C_{10}H_{21}$	4	240—243 (1)	1,4950	$C_{23}H_{39}NO_5$	67,4	9,8	3,6	67,5	9,5	3,4	1773	1738	1680	34
XII	$C_6H_5CH_2$	4	240—242 (2)	1,5480†	$C_{19}H_{23}NO_5$	66,1	7,1	4,1	66,1	6,6	4,0	1775	1730	1658	29
XIII	C_8H_{17}	5	239—240 (1)	1,4895	$C_{22}H_{37}NO_5$	66,5	9,1	3,9	66,8	9,3	3,5	1775	1732	1658	45
XIV	C_9H_{19}	5	219—222 (1)	1,4910	$C_{23}H_{39}NO_5$	67,4	9,2	3,6	67,5	9,2	3,4	1762	1730	1686	45
XV	$C_{10}H_{21}$	5	257—260 (1)	1,4940	$C_{24}H_{41}NO_5$	68,6	9,2	3,4	68,1	9,7	3,3	1775	1730	1690	32
XVI	$C_6H_5CH_2$	5	246—248 (2)	1,5375†	$C_{20}H_{25}NO_5$	66,9	6,9	3,9	66,8	6,9	3,9	1758	1730	1686	28

---

*Spectra taken on a IKS-14 instrument in a thin layer.

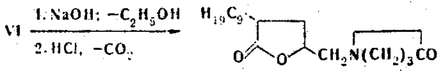
†n_D^{50}.



V-XVI XVII-XX

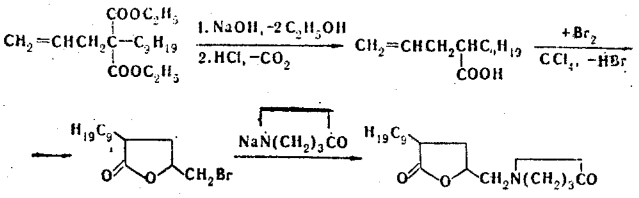
V $R=C_8H_{17}$, $n=3$; VI $R=C_9H_{19}$, $n=3$; VII $R=C_{10}H_{21}$, $n=3$; VIII $R=C_6H_5CH_2$, $n=3$;
IX $R=C_8H_{17}$, $n=4$; X $R=C_9H_{19}$, $n=4$; XI $R=C_{10}H_{21}$, $n=4$; XII $R=C_6H_5CH_2$, $n=4$;
XIII $R=C_8H_{17}$, $n=5$; XIV $R=C_9H_{19}$, $n=5$; XV $R=C_{10}H_{21}$, $n=5$; XVI $R=C_6H_5CH_2$, $n=5$;
XVII $R=C_8H_{17}$; XVIII $R=C_9H_{19}$; XIX $R=C_{10}H_{21}$; XX $R=C_6H_5CH_2$.

In order to prove the structure of compounds (V-XVI), 2-ethoxycarbonyl-2-nonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactone (VI) was subjected to alkaline hydrolysis:



XXI

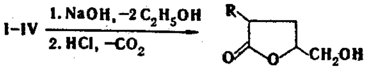
Compound (XXI) was also obtained by independent synthesis, in the following way [4]:



XXI a

The 2-nonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactones obtained by the different methods showed no depression of the melting points. The IR spectra of compound (XXI) lacked the absorption band at 1732 cm^{-1} that is characteristic for an ester carbonyl and showed bands at 1770 and 1684 cm^{-1} which are characteristic for lactone and lactam carbonyls, and in the spectra of compound (XXIa) there were analogous bands at 1765 and 1680 cm^{-1}.

To establish the structure of compounds (XVII-XX), the alkaline hydrolysis of (I-IV) was performed, as a result of which the same 2-alkyl- and 2-benzyl-5-hydroxy-γ-valerolactones (XVIIa-XXd) (Table 4) were obtained; mixtures of them with the corresponding compounds (XVII-XX) gave no depression of the melting points.



XVII a-XX

I, XVII a $R=C_8H_{17}$; II, XVIII b $R=C_9H_{19}$;
III, XIX c $R=C_{10}H_{21}$; IV, XX d $R=C_6H_5CH_2$

In the IR spectra of (XVII-XX) (Table 3) and of (XVIIa-XXd) (Table 4), the bands of C=O and OH stretching vibrations were observed. A broad band in the 3500-3100 cm^{-1} region with a clearly isolated doublet probably indicating different forms of association corresponds to the stretching vibration of the hydroxy groups of these compounds [apart from (XX) and (XXd), which are liquids]. Tables 3 and 4 give the maxima of the doublets.

The formation of the 2-alkyl- and 2-benzyl-5-hydroxy-γ-valerolactones (XVII-XX) as byproducts takes place under the action of the lactams. When the epoxide is heated separately or with catalytic amounts of water at 200-210°C in the absence of a lactam, the initial epoxide undergoes no changes.

Judging from the experimental results, the lactam acts both on the oxirane ring of the alkyl- and benzylglycidylmalonic ester and on one of the ethoxycarbonyl groups. Apparently, the lactam converts the ethoxycarbonyl group into an acid group which, under the experimental conditions, decarboxylates, and the lactam itself is converted into the N-ethyl derivative. A similar effect on an ester group has been reported previously when ethyl esters of 2-substituted γ-butyrolactone-4-carboxylic acids were treated with potassium phthalimide. Under these conditions, phthalimide derivatives were obtained in low yields. The main

TABLE 3. 2-Alkyl- and 2-Benzyl-5-hydroxy-γ-valerolactones

Compound	R	mp, °C (solvent for crystallization)	bp, °C (pressure, mm)	Empirical formula	Found, %		Calculated, %		IR spectra, ν_{max}, cm^{-1}		Yield, % (at n)*
					C	H	C	H	C=O	OH	
XVII	C_8H_{17}	72 (petroleum ether)	172—174 (1)	$C_{13}H_{24}O_3$	68,5	10,8	68,4	10,5	1758	3332, 3236	37 (3) 44 (4) 20 (5)
XVIII	C_9H_{19}	76 (petroleum ether)	176—177 (1)	$C_{14}H_{26}O_3$	70,0	11,0	69,4	10,7	1754	3324, 3240	42 (3) 44 (4) 30 (5)
XIX	$C_{10}H_{21}$	79 (acetic acid)	183—185 (1)	$C_{15}H_{28}O_3$	70,7	10,9	70,3	10,9	1756	3328, 3166	64 (3) 25 (4) 18 (5)
XX†	$C_6H_5CH_2$	—	175—176 (2)	$C_{12}H_{14}O_3$	70,1	6,7	69,9	6,8	1760	3416	48 (3) 41 (4) 21 (5)

---

* Yields calculated according to the amounts of substances obtained in the reaction of the epoxide with pyrrolidinone (n = 3), piperidinone (n = 4), and caprolactam (n = 5).

† d_4^{20} 1.1870, n_D^{20} 1.5435. Found: MR_D 54.72. $C_{12}H_{14}O_3$. Calculated: MR_D 54.99. In the spectra of (XX), a frequency of 1605 cm^{-1}, characteristic for the benzene ring, was found. The spectra were taken on a IKS-14 instrument in paraffin oil.

TABLE 4. 2-Alkyl- and 2-Benzyl-5-hydroxy-γ-valerolactones

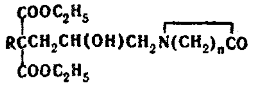
Compound	R	mp, °C (solvent for crystallization)	bp, °C (pressure, mm)	Empirical formula	Found, %		Calculated, %		IR spectra, ν_{max}, cm^{-1}		Yield, %
					C	H	C	H	C=O	OH	
XVIIa	C_8H_{17}	72 (petroleum ether)	172—174 (1)	$C_{13}H_{24}O_3$	68,3	10,8	68,4	10,5	1756	3328, 3166	67
XVIIIb	C_9H_{19}	76 (petroleum ether)	176—177 (1)	$C_{14}H_{26}O_3$	68,8	10,7	69,4	10,7	1756	3320, 3240	89
XIXc	$C_{10}H_{21}$	79 (acetic acid)	204 (3)	$C_{15}H_{28}O_3$	70,5	10,7	70,3	10,9	1756	3324, 3150	83
XXd*	$C_6H_5CH_2$	—	175—176 (2)	$C_{12}H_{14}O_3$	70,1	6,8	69,9	6,8	1760	3440	65

---

* d_4^{20} 1.1872, n_D^{20} 1.5441. Found: MR_D 54.78. $C_{12}H_{14}O_3$. Calculated: MR_D 54.99. In the spectra of (XXd) a frequency of 1605 cm^{-1} characteristic for the benzene ring was observed. The spectra were taken on a IKS-14 instrument in paraffin oil.

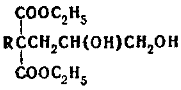
process was the alkylation of the potassium phthalimide with the ethoxycarbonyl part of the ester-lactone. However, in our case it was impossible to detect N-ethyl derivatives of the lactams in the mass of excess lactam distilled off.

The final stage of the opening of the oxirane ring takes place by the action of two competing groups $-\overline{N(CH_2)_nCO}$ and $-OH$, which also explains the formation of the intermediate systems:



$$R\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}CH_2CH(OH)CH_2\overline{N(CH_2)_nCO}$$

A

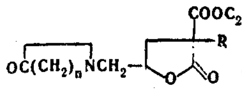


$$R\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}CH_2CH(OH)CH_2OH$$

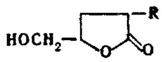
B

It might be expected that if no water were used, the reaction should take place only with the formation of the product of lactam addition, but in this case resinification products are formed in large amount.

The action of the lactam on one of the ethoxycarbonyl groups in A or B or in the products of their cyclization is not equiprobable, since only in the cyclized product from B is there no ethoxycarbonyl group.

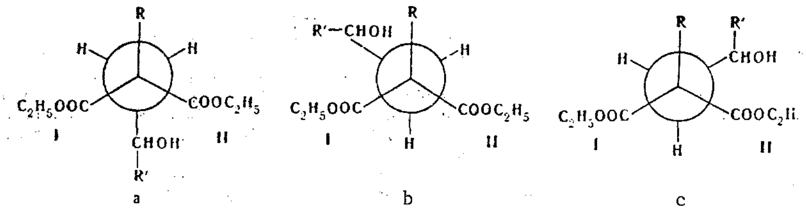


and



The explanation of this consists in a consideration of steric factors acting in the intermediate compounds A and B or in the products of their cyclization.

Compounds are obtained with two asymmetric centers, i.e., in application to the cyclic structures it is possible for cis-or trans-isomers to be formed. Judging from the experimental facts, it may be assumed that only one isomer is obtained in each case, i.e., cyclization takes place in stereodirected fashion. Apparently, in reactions involving cleavage of an epoxide ring with cyclization to a lactone, we have a peculiar combination of steric and energy conditions which keep a definite ethoxycarbonyl group in contact with the hydrogen atom of the hydroxy group in intermediate compound A or B, which we shall examine with A as example. On modeling this structure, the following possibilities of the appearance of a gauche conformation are found (only the hydrogen bonds between the groups $-OH------\underset{|}{O}COC_2H_5$ are considered, since it is the reaction of just these groups that leads to the formation of the γ-lactone ring):



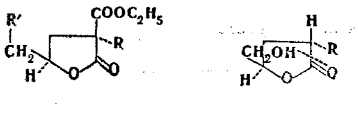
a

b

c

$R = C_8H_{17}, C_9H_{19}, C_{10}H_{21}, C_6H_5CH_2$; $R' = CH_2\overline{N(CH_2)_nCO}$

With the participation of a hydrogen bond in both cases, the appearance of seven-membered cyclic transition states is possible, but stabilization of the transition states through the formation of a γ-lactone ring with a participation of either of the ethoxycarbonyl groups is not equiprobable. The formation of a ring with ethoxy group I in conformation b is energetically less favorable since under these circumstances the bulky substituents R and R', between which any interaction (apart from van der Waals interaction) is excluded, occupy the trans position with respect to the plane of the ring, while cyclization through ethoxycarbonyl groups I or II in conformation a and through ethoxycarbonyl group II in conformation c leads to a ring in which the voluminous substituents are present in the cis position.



Similar considerations are also applicable to B taking into account only the fact that the CH_2OH group reacts with the carbonyl of the lactone ring.

It has already become clear why there is no ester group in compounds (XVII-XX) and why the reaction of the lactam is exclusively with the same group in compounds (V-XIV). The presence of an ethoxycarbonyl group in some and its absence from other compounds is evidence in favor of the trans structure of the products obtained, since in compounds (V-XVI) the voluminous substituents $-CH_2-R'$ block the approach of the lactam to the ethoxycarbonyl group, while in (XVII-XX) the comparatively small hydroxymethyl group, connected by interaction with the carbonyl lactone, does not prevent this interaction.

EXPERIMENTAL

Alkyl- and Benzylglycidylmalonic Esters (I-IV). These were obtained by the reaction of alkyl- and benzylmalonic esters with epichlorohydrin by a known procedure [2] (Table 1).

2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactones, 2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-4-(2-oxopiperidinomethyl)-γ-butyrolactones, 2-Alkyl- and 2-Benzyl-2-ethoxycarbonyl-5-(2-oxoazepin-1-yl)-γ-valerolactones (V-XVI), and 2-Alkyl- and 2-Benzyl-5-hydroxy-γ-valerolactones (XVII-XX). A mixture of 1 mole of (I-IV), 4 moles of a lactam (pyrrolidinone, piperidinone, or caprolactam), and 3-4 drops of water was heated at 200-210°C for 10 h and was then distilled in vacuum; the first fraction taken off was the excess of lactam and the second fraction consisted of compounds (XVII-XX) (they crystallized in the receiver) (Table 3), while the third fraction consisted of (V-XVI) (Table 2).

2-Nonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactone (XXI). A mixture of 10.4 g (0.027 mole) of (VI) and 3.27 g (0.081 mole) of a 50% aqueous solution of caustic soda was heated in the water bath for 6 h, cooled, and worked up by known methods [5]. Distillation yielded 5.24 g (62%) of (XXI) with bp 228-230°C (1 mm), n_D^{20} 1.4875. The substance crystallized in the course of time, mp 63°C (from ethanol). Found %: C 70.1; H 10.2; N 4.55. $C_{18}H_{31}NO_3$. Calculated %: C 69.9; H 10.03; N 4.53.

2-Nonyl-4-(2-oxopyrrolidinomethyl)-γ-butyrolactone (XXIa). A mixture of 1.18 g (0.011 mole) of the sodium derivative of pyrrolidone, 14.6 ml of dry N,N-dimethylformamide, and 3.5 g (0.01147 mole) of 5-bromo-2-nonyl-γ-valerolactone was boiled for 5 h and was then cooled to room temperature and filtered, the dimethylformamide was driven off, the residue was dissolved in dry acetone, the solution was filtered, the acetone was driven off, and the residue was distilled to give 1.3 g (37%) of (XXIa), bp 227-230°C (1 mm), n_D^{20} 1.4880. In the course of time, the product crystallized; mp 63°C (from ethanol). Found %: C 69.1; H 10.3; N 4.45. $C_{18}H_{31}NO_3$. Calculated %: C 69.9; H 10.3; N 4.45.

2-Alkyl- and 2-Benzyl-5-hydroxy-γ-valerolactones (XVIIa-XXd). A mixture of 1 mole of an alkyl- or benzylglycidylmalonic ester (I-IV) and 3 moles of 50% aqueous caustic soda was heated in the water bath for 6 h, cooled, worked up by known methods [5], and distilled to give (XVIIa-XXd), which crystallized in the receiver (Table 4).

LITERATURE CITED

1. M. F. Shostakovskii, F. P. Sidel'kovskaya, and M. G. Zelenskaya, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 4, 738 (1959).
2. É. G. Mesropyan, Z. T. Karapetyan, and M. T. Dangyan, Arm. Khim. Zh., 22, 904 (1969); 24, 583 (1971).
3. S. V. Arakelyan and M. T. Dangyan, Nauchnye Trudy Erevansk. Gos. Un-ta, Khim. Nauk, 44, 35 (1954); 53, 3 (1956); 60, 17 (1957).
4. S. V. Arakelyan, Dissertation, Erevan State University (1961).
5. A. N. Kost, ed., Organicum: Practical Handbook of Organic Chemistry, Pergamon Press, Oxford (1973).