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HOMOLYTIC ADDITION OF CYCLIC ETHERS TO CROTONIC ACID

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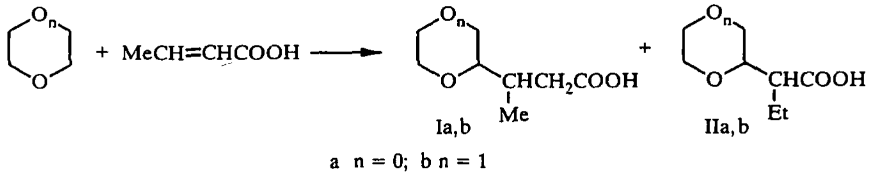
It has been found that the route of addition of tetrahydrofuran and dioxane to crotonic acid depends on the temperature of the reaction. A feature of the synthesized oxacycloalkylbutyric acids is the existence of an intramolecular hydrogen bond involving the oxygen atom of the heterocycle..

We have previously developed a method for preparing tetrahydrofurylalkanoic acids by homolytic addition of tetrahydrofuran to a series of unsaturated acids (acrylic, methacrylic, allylacetic, undecenoic). The reaction occurs upon heating a mixture of tetrahydrofuran, the unsaturated acid, and the initiator di-*tert*-butyl peroxide (DTBP) in proportions 75-100:1:0.1-0.12 at 200-300°C in an autoclave at 50-80 atmospheres [1, 2]. The use of high temperatures and a large excess of cyclic ether was necessary to suppress telo- and polymerization processes.

The aim of this investigation was to study the addition of tetrahydrofuran and dioxane to crotonic acid. As shown by the results in Table 1, in contrast to reaction with the readily polymerized α,β-unsaturated acids (acrylic, methacrylic), the reaction of tetrahydrofuran with crotonic acid under conditions described above occurs in high product yield (60-65%) even at 130-150°C (in an autoclave). Moreover, the reaction can occur without the initiator but at higher temperature and with decreased yield. In addition, it is possible to use a significantly smaller tetrahydrofuran to crotonic acid ratio. Under analogous conditions, the reaction with dioxane gives lower yields of addition product.

A feature of the reaction of cyclic ethers with crotonic acid is the fact that, at 130-200°C, a mixture of two isomers is formed, the ratio of isomers depending on the reaction temperature. At lower temperatures the regioselectivity of the process is increased, but in all cases isomer I predominates.



The ratio of isomers I / II is determined by GLC.

Bearing in mind the relative stability of crotonic acid towards polymerization, we have developed a more convenient method for carboxyalkylation of tetrahydrofuran and dioxane by crotonic acid without using an autoclave, at atmospheric pressure, and at temperatures of 66 and 100°C respectively (i.e. the boiling point of the cyclic ether). The reaction is carried out by stepwise addition of a solution of crotonic acid and the initiator (benzoyl peroxide in the cyclic ether) to the refluxing cyclic ether over 35-40 h. With these conditions, the addition occurs selectively to give exclusively the isomers I in 60-65% (Ia) and 30-37% (Ib) yields.

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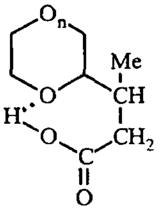
A feature of the obtained 3-(α-tetrahydrofuryl)- (Ia) and 3-dioxanyl (Ib) butyric acids is the fact that the PMR spectra of these acids show a signal for the CH_3 group which is an unsymmetrical triplet (Ia) or a pair of doublets (Ib) instead of the expected doublet. GLC of the reaction products show that they are the single acids indicated, hence we infer that such a PMR picture is related to hindered rotation of the CH_3 group. One reason for this may arise from an intramolecular hydrogen bond of the type



Formation of hydrogen bonds with acidic compounds, as is known, is extremely characteristic of simple ethers, especially of dioxane. The latter forms complexes (dioxanates) even with such weak acids as o-chlorophenol [3, 4]. In order to prevent formation of an intramolecular hydrogen bond, we have synthesized methyl esters of acids Ia and Ib (compounds IIIa and IIIb) by exhaustive methylation of Ia and Ib with diazomethane and addition of tetrahydrofuran and dioxane to methyl crotonate. In this way we found that the reaction with methyl crotonate proceeds in higher yield than with crotonic acid, especially in the case of dioxane. Evidently formation of an intermolecular hydrogen bond between the oxygen atom of the cyclic ether and the carboxyl group of crotonic acid lowers the reactivity of the C=C bond due to decreased influence of the carboxyl group [5].. In the PMR spectra of methyl esters IIIa and IIIb, the CH_3 group signal appears as a symmetrical doublet. In addition, the preparation of anilides of acids Ia and Ib with 2,5-xylidine have been prepared using the Einhorn method [6] because acid Ia and Ib chlorides could not be prepared by conventional methods due to the acidophobicity of tetrahydrofuran and dioxane rings. In the PMR spectra of anilides the side chain CH_3 group signal is also seen as a doublet. Hence, the formation of an intramolecular hydrogen bond in acids Ia and Ib may be considered to be proved.

TABLE 1. Addition of Tetrahydrofuran and Dioxane to Crotonic Acid and its Methyl Ester

Molar proportions of cyclic ether : crotonic acid (ester) : initiator	T, °C	Reaction time, h	Yield of acids (I + II), % (ratio)
	Tetrahydrofuran		
100 : 1: 0,1	200	6	63 (1,4 : 1)
50 : 1: 0,1	200	6	65 (1,4 : 1)
25 : 1: 0,1	200	6	42 (1,6 : 1)
100 : 1 —	200	6	25 (1,5 : 1)
50 : 1: 0,1	130...150	6	60 (3 : 1)
50 : 1: 0,1	66	41	60
50 : 1: 0,1*, *2	66	41	72
	Dioxane		
100 : 1: 0,1	200	6	44 (4 : 1)
100 : 1 —	200	6	Traces
50 : 1: 0,1	200	6	41(4,5 : 1)
50 : 1: 0,1	130...150	6	31(9 : 1)
50 : 1: 0,1*	100	41	23
50 : 1: 0,1*, *2	100	41	35

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* Initiator benzoyl peroxide, elsewhere - di-*tert*-butyl peroxide.

*2 With methyl crotonate, elsewhere with crotonic acid.

TABLE 2. Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % Calculated, %			Bp (mm Hg) or mp, °C	PMR Spectra ($CDCl_3$, δ, ppm)				
		C	H	N		CH_3,chain	α-CH, ring	β-CH, ring	CH-CH_2, chain	other protons
Ia	$C_8H_{14}O_3$	60,76 60,40	8,86 9,21	—	136 (2)	0,76...1,0 (3H, t)	3,5...3,9 (3H, m)	1,5...2,5 (7H, m)	—	—
Ib	$C_8H_{14}O_4$	55,17 55,30	8,04 7,92	—	160...162 (6)	0,8...1,0 (3H, two d)	3...3,75 (7H, m)	—	2,1...2,6 (3H, m)	—
IIIa	$C_9H_{16}O_3$	62,79 62,03	9,30 9,04	—	115 (2)	0,8...0,95 (3H, d)	3,5...3,7 (3H, m)	1,5...2,5 (7H, m)	—	3,6 (3H, s, OCH_3)
IIIb	$C_9H_{16}O_4$	55,44 55,17	8,51 8,74	—	128 (2)	1...1,1 (3H, d)	3,2...3,7 (7H, m)	—	1,2...1,8 (2H, m) 2,5...2,7 (1H, m)	3,6 (3H, s, OCH_3)
IV	$C_{16}H_{23}NO_2$	73,88 73,56	9,10 8,81	5,69 5,36	104...105 ethanol	0,8...0,95 (3H, d)	3,3...3,85 (3H, m)	—	1,5...2,5 (7H, m)	2,1 (3H, s, Ar-CH_3) 2,3 (3H, s, Ar-CH_3)
V	$C_{16}H_{23}NO_3$	69,55 69,31	8,59 8,30	5,25 5,05	133...135 ethanol	0,95...1,1 (3H, d)	3,25...3,7 (7H, m)	—	2,1...2,6 (3H, m)	2,1 (3H, s, Ar-CH_3) 2,3 (3H, s, Ar-CH_3)

EXPERIMENTAL

PMR spectra were recorded on a Tesla-567 instrument (100 MHz, internal standard HMDS) and mass spectra were taken on an MX-1310 mass spectrometer. GLC analysis of the reaction mixtures was performed on a Biochrom chromatograph using a glass column (200 x 0.3 cm) with 5% SKTFT on Inerton AW (0.100-0.125 mesh).

The reactions at 130-200°C were carried out in a 3 liter steel autoclave (filling coefficient 0.6-0.8) and at 66-100°C in a three-necked flask with two dropping funnels. After completion of the reaction, the main amount of cyclic ether was distilled off, the residue analyzed by GLC (internal standard acetophenone) and distilled *in vacuo*. For separation of the pure acids the obtained crude fractions were treated with saturated $NaHCO_3$ solution, this solution was washed several times with benzene, and then acidified with dilute hydrochloric acid and extracted with benzene. The benzene extracts were dried and, after distillation of benzene, distilled *in vacuo*.

Addition of tetrahydrofuran to crotonic acid. A. To refluxing THF (325 ml, 4 mole) crotonic acid (8.6 g, 0.1 mole) in THF (40 ml, 0.5 mole) and benzoyl peroxide (2.42 g, 0.01 mole) in THF (40 ml, 0.5 mole) were added over 40 h after which the reaction mixture was refluxed for a further 1 h. Distillation *in vacuo* (5 mm) gave a fraction (5.2 g, bp 80-125°C) which was a mixture of benzoic and crotonic acids and a fraction (12 g, bp 155-165°C) which was acid Ia (83%); (GLC data).

B. A mixture of tetrahydrofuran (1620 ml, 20 mole), crotonic acid (17.2 g, 0.1 mole) and DTBP (2.92 g, 0.02 mole) was heated for 6 h in an autoclave at 200°C. Distillation *in vacuo* gave a fraction (23.2 g, bp 163-165°C) containing a mixture of acids Ia and IIa (94%). The acids were purified by reprecipitation from $NaHCO_3$ solution (acid IIa could not be obtained in the pure state; it was identified in mixture on the basis of GLC and mass spectral data).

Addition of dioxane to crotonic acid. A. Similarly to the above from dioxane (425 ml, 5 mole), crotonic acid (8.6 g, 0.1 mole), and benzoyl peroxide (2.42 g, 0.01 mole) at 100°C for 41 h a fraction (5.3 g, bp 160-175°C, 5 mm) was obtained which contained acid Ib (80%); (GLC data).

B. A mixture of dioxane (1275 ml, 15 mole), crotonic acid (12.9 g, 0.15 mole), and DTBP (2.19 g, 0.015 mole) was heated at 200°C for 6 h to give, after the appropriate work-up, a fraction (13.5 g, bp 165-175°C, 5 mm) containing a mixture of acids Ib and IIb (91%). Acid IIb could not be obtained in the pure state (as for Ib) but its formation was proved by GLC and mass spectral data.

General method for preparing anilides of acids Ia and Ib. Thionyl chloride (0.3 g) was added slowly to a mixture (cooled in ice-salt) of 2,5-xylidine (1.5 mmole), the corresponding acid (1.9 mmole), and pyridine (10 ml). The product was held for 1 h in the cold and then 4 h at room temperature after which it was poured into cold water acidified with hydrochloric acid. The mixture was extracted with benzene and, after removal of benzene, the brown crystalline mass was treated with saturated $NaHCO_3$ solution, washed with water, and filtered off. To purify the obtained anilide it was necessary to reflux a solution of it in alcohol with activated carbon. Using this method, acid Ia (0.3 g, 1.9 mmole) and 2,5-xylidine (0.18 g, 1.5 mmole) gave 2,5-dimethylanilide of 3-tetrahydrofuranylbutyric acid (IV, 0.26 g, 68%). Similarly acid Ib (0.33 g, 1.9 mmole) and 2,5-xylidine (0.18 g, 1.5 mmole) gave 2,5-dimethylanilide of 3-dioxanylbutyric acid (V, 0.21 g, 57%). The boiling points of the anilides obtained as well as their PMR spectra are given in Table 2.

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