TOTAL SYNTHESIS AND PROPERTIES OF PROSTAGLANDINS

30.* MODIFICATION OF (1S,5R)-2-OXABICYCLO[3.3.0]-6-OCTEN-3-ONE AT THE α-CARBON ATOM

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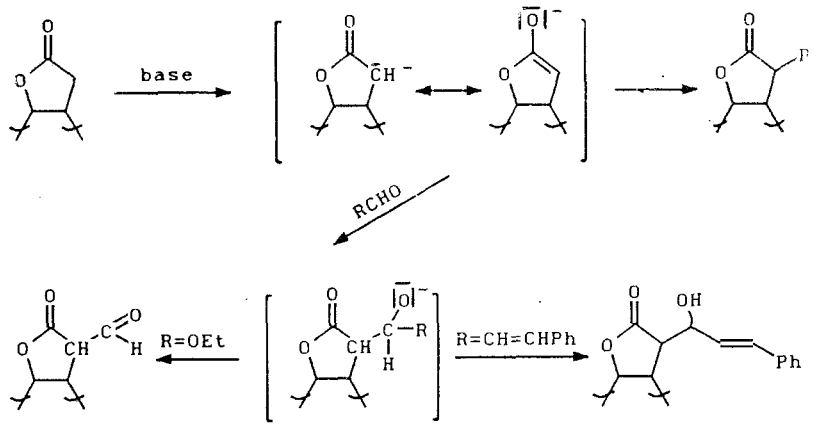
Derivatives of α-alkyl-, α-alkylidene-, and α-hydroxymethylene-2-oxabicyclo[3.3.0]-6-octen-3-one were obtained. The possibility of functional substitution of the bicyclic γ-lactones at the α position to the carbonyl group was thereby demonstrated.

Many natural compounds contain an α-alkyl- and more frequently an α-methylene-γ-lactone fragment, responsible for their biological activity [2-4]. In the last decade a considerable number of publications have been devoted to the development of suitable methods for the synthesis of α-alkylidene and hydroxyalkylidene derivatives of γ-butyrolactone and lactones condensed with six-, seven-, and 10-membered rings [5-11]. However, there are hardly any data on α-alkylidene-γ-lactones condensed with a five-membered ring. From the standpoint of the biological characteristics of the products it seemed of interest to combine such a lactone fragment with the structural elements of prostaglandins in a single molecule. For the initial investigations we used (+)-2-oxabicyclo[3.3.0]-6-octen-1-one (I) (subsequently, the γ-lactone), which is the opposite enantiomer of the lactone widely used in the synthesis of natural prostaglandins. Our modification is based on the formation of the intermediate carbanion, which then either reacts with the alkylating agents (direct alkylation) or adds to the C=O bonds of ethyl formate (ester condensation) or the corresponding aldehyde (aldol condensation):



The carbanion (or the enolate of the ion) is formed by the action of bases and of lithium or sodium amides in particular.

In the literature the direct α-alkylation of γ-lactones through their metal enolates has been mostly described for γ-butyrolactone [12, 13]. The yields of this reaction fluctuate in a wide range, depending on the employed bases and on the alkylating agents.

*For Communication 29, see [1].

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TABLE 1. Yields and Characteristics of the Synthesized Compounds (III-VIII, X, XII, XIV-XVII)

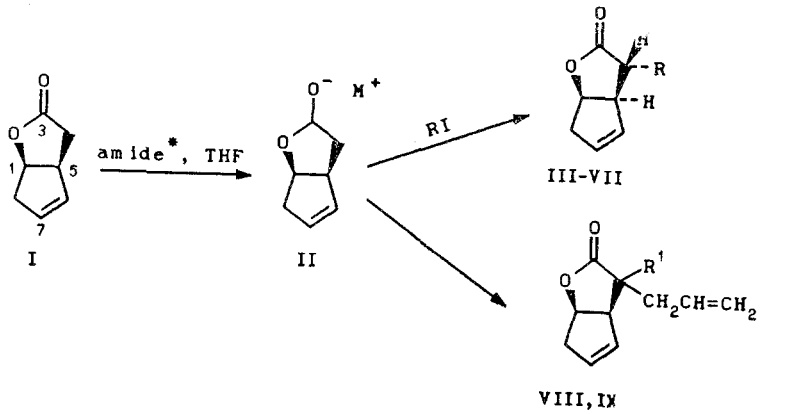
Compound	R_f (system)*	K (system)*	IR spectrum, ν, cm^{-1}†	Product yield, %	Recovery of initial substance, %
III	0,44 (A)	2,83 (B)	1765 (CO)	42	45
IV	0,73 (E)	1,30 (B)	1765 (CO)	50	27
V	0,68 (G)	0.76 (B)	1765 (CO)	30	52
VI	0,66 (E) 2×	—	—	31	63
VII	0,46 (E)	0.78 (A)	1770 (CO); 1740 ($COOC_2H_5$)	37	32
VIII	0,58 (E)	1,79 (B) 1,14 (B)	1770 (CO)	60	11
Xa	0,27 (E)	—	3600 (OH); 1760 (CO)	27	—
Xb	0,22 (E)	—	3600 (OH); 1760 (CO)	43	—
XIIa	0,42 (F)	—	1745 (CO); 1680 (C=CH)	29 (13)‡	—
XIIb	0,37 (F)	—	1745 (CO); 1680 (C=CH)	39 (50)‡	—
XIV	0,35 (E)	—	—	87	—
XV	0,47 (E)	3,04 (A)	1735...1750 (CO, $COOC_2H_5$); 1680 (C=CH)	63.7	—
XVI	0,51 (C)	5,40 (A)	1740 (CO, $COOCH_3$); 1680 (C=CH)	56.5	—
XVII	0,40 (D)	2,96 (A)	1740 (CO, $COOC_2H_5$); 1680 (C=CH)	39,5	—

*Solvent systems hexane—isopropyl alcohol 90:10 (system A), 95:5 (B); hexane—ethyl acetate, 1:1 (C), 1.5:1 (D), 2:1 (E), 3:1 (F), 4:1 (G). †The IR spectra of compounds (XV-XVII) were recorded in Nujol, and the others were recorded in chloroform solution. ‡The yields of the compounds obtained from compound (Xa) and from compound (Xb) (in parentheses).

The compounds we obtained by direct alkylation of the lactone (I) are presented in scheme 1. The α-methyl-, α-ethyl-, α-butyl-, and α-alkoxycarbonylmethyl-γ-lactones (III-VII) were obtained by alkylation of the lithium enolate of the lactone (II) with the corresponding alkyl iodide or iodoacetic ester in THF with the addition of HMPTA. The lithium enolate was obtained by the action of lithium diisopropylamide on the lactone (I) in THF at −70°C.

The α-allyl derivative (VIII) was obtained through the sodium enolate, obtained by the reaction of the lactone with sodium bistrimethylsilylamide.

Scheme 1



III R=CH_3; IV R=C_2H_5; V R=C_4H_9; VI R=CH_2COOCH_3; VII R=$CH_2COOC_2H_5$; VIII R^1=H; IX R^1=$CH_2CH=CH_2$; M^+=Li or Na

As bases we also used other lithium amides, i.e., isopropylcyclohexyl-, dicyclohexyl-, bistrimethylsilyl-, and 2,2,6,6-tetramethylpiperidylamides. However, the best product yields were obtained with the above-mentioned amides. As seen from Table 1, the yields from the α-substituted γ-lactones were relatively low, and quite a large amount of the unreacted initial

TABLE 2. PMR Spectra of the Synthesized Compounds (III-XII, XIV, XVII)

Compound	Chemical shift, δ, ppm
III	5,78 (1H, m, 7-H); 5,62 (1H, m, 6-H); 5,15 (1H, m, 1-H); 3,17 (1H, m, 5-H); 2,70 (2H, m, 8-H); 2,55 (1H, m, 4-H); 1,37 (3H, d, CH_3)
IV	5,78 (1H, m, 7-H); 5,58 (1H, m, 6-H); 5,10 (1H, m, 1-H); 3,23 (1H, m, 5-H); 2,72 (2H, m, 8-H); 2,42 (1H, m, 4-H); 1,63 ... 1,90 (2H, m, CH_2CH_3); 1,09 (3H, t, CH_2CH_3)
V	5,77 (1H, m, 7-H); 5,58 (1H, m, 6-H); 5,10 (1H, m, 1-H); 3,22 (1H, m, 10-H); 2,70 (2H, m, 8-H); 2,43 (1H, m, 4-H); 1,56 ... 1,83 (2H, m, $CH_2(CH_2)_2CH_3$); 1,30 ... 1,50 (4H, m, $CH_2(CH_2)_2CH_3$); 0,95 (3H, t, CH_3)
VI	5,80 (1H, m, 7-H); 5,68 (1H, m, 6-H); 5,20 (1H, m, 1-H); 3,74 (3H, s, $COOCH_3$); 3,28 (1H, m, 5-H); 2,63 ... 2,88 (5H, m, 4-H, 8-H, CH_2CO)
VII	5,77 (1H, m, 7-H); 5,66 (1H, m, 6-H); 5,20 (1H, m, 1-H); 4,20 (2H, q, CH_2CH_3); 3,30 (1H, m, 5-H); 2,64 ... 2,88 (5H, m, 4-H, 8-H, CH_2CO); 1,30 (3H, t, CH_2CH_3)
VIII	5,73 ... 5,98 (2H, m, 7-H, CH_2=CH—CH_2); 5,58 (1H, m, 6-H); 5,20 (2H, m, CH_2—CH=CH_2); 5,12 (1H, m, 1-H); 3,28 (1H, m, 5-H); 2,55 (2H, m, 4-H, CH_2—CH=CH_2); 2,72 (2H, m, 8-H); 2,41 (1H, m, CH_2—CH=CH_2)
IX	5,71 ... 5,98 (4H, m, 7-H, 6-H, CH_2=CH—CH_2); 5,17 (4H, m, CH_2—CH=CH_2); 5,01 (1H, m, 1-H); 3,25 (1H, m, 5-H); 2,67 (2H, m, 8-H); 2,54 (1H, dd, CH_2—CH=CH_2); 2,38 (2H, d, CH_2—CH=CH_2); 2,31 (1H, dd, CH_2—CH=CH_2)
Xa	7,25 ... 7,43 (5H, m, C_6H_5); 6,76 (1H, d, 3′-H); 6,25 (1H, dd, 2′-H); 5,78 (1H, m, 7-H); 5,55 (1H, m, 6-H); 5,15 (1H, m, 1-H); 4,90 (1H, m, 1′-H); 3,54 (1H, m, 5-H); 2,68 (2H, m, 8-H); 2,56 (1H, m, 4-H)
Xb	7,25 ... 7,45 (5H, м, C_6H_5); 6,72 (1H, d, 3′-H); 6,34 (1H, dd, 2′-H); 5,77 (1H, m, 7-H); 5,59 (1H, m, 6-H); 5,11 (1H, m, 1-H); 4,64 (1H, t, 1′-H); 3,48 (1H, m, 5-H); 2,68 (2H, m, 8-H); 2,75 (1H, m, 4-H)
XIa	7,27 ... 7,44 (5H, m, C_6H_5); 6,71 (1H, d, 3′-H); 6,20 (1H, dd, 2′-H); 5,83 (2H, m, 7-H, 6-H); 5,59 (1H, m, 1′-H); 5,12 (1H, m, 1-H); 3,57 (1H, m, 5-H); 2,82 (1H, m, 4-H); 2,72 (2H, m, 8-H); 2,14 (3H, s, $COCH_3$)
XIb	7,25 ... 7,45 (5H, m, C_6H_5); 6,73 (1H, d, 3′-H); 6,33 (1H, dd 2′-H); 5,82 (2H, m, 7-H, 6-H); 5,60 (1H, m, 1′-H); 5,05 (1H, m, 1-H); 3,48 (1H, m, 5-H); 2,90 (1H, m, 4-H); 2,72 (2H, m, 8-H); 2,14 (3H, s, $COCH_3$)
XIIa	8,20 (1H, m, 1′-H); 7,22 ... 7,54 (5H, m, C_6H_5); 6,80 (2H, m, 3′-H, 2′-H); 5,81 (1H, m, 7-H); 5,60 (1H, m, 6-H); 5,12 (1H, m, 1-H); 4,05 (1H, m, 5-H); 2,70, 2,81 (2H, m, 8-H)
XIIb	7,30 ... 7,52 (5H, m, C_6H_5); 7,22 (1H, m, 1′-H); 6,98 (2H, m, 3′-H, 2′-H); 5,84 (1H, m, 7-H); 5,70 (1H, m, 6-H); 5,17 (1H, m, 1-H); 4,28 (1H, m, 5-H); 2,78, 2,88 (2H, m, 8-H)
XIV	7,45 (1H, d, CHOH); 5,87, 5,75 (1H, m, 7-H); 5,57 (1H, m, 6-H); 5,12 ... 5,25 (1H, m, 1-H); 3,98 ... 4,07 (1H, m, 5-H); 3,6 (1H, d, OH); 2,67, 2,88 (2H, m, 8-H)
XV	7,16 (1H, d, =CH); 5,76 (2H, m, 6-H, 7-H); 5,12 (1H, t, 1-H); 4,55 (2H, s, O—CH_2CO); 4,27 (2H, q, CH_2CH_3); 4,16 (1H, m, 5-H); 2,63 ... 2,85 (2H, m, 8-H); 1,32 (3H, t, CH_2CH_3)
XVI	7,25 (1H, d, =CH); 5,72 (2H, m, 6-H, 7-H); 5,08 (1H, t, 1-H); 4,05 ... 4,1 (3H, t, m, 5-H, O—CH_2); 3,68 (3H, s, $COOCH_3$); 2,80 (1H, m, 8-H); 2,67 (1H, m, 8-H); 2,45 (2H, t, CH_2CO); 2,05 (2H, q, $CH_2CH_2CH_2CO$)
XVII	7,25 (1H, d, =CH); 5,70 (2H, m, 6-H, 7-H); 5,08 (1H, t, 1-H); 4,17 (2H, q, CH_2CH_3); 4,05 (3H, m, 5-H, O—CH_2); 2,62 ... 2,84 (2H, m, 8-H); 2,36 (2H, t, CH_2CO); 1,73 (4H, m, $(CH_2)_2$); 1,25 (3H, t, CH_2CH_3)
XVa	7,41 (1H, d, =CH); 5,73 (2H, m, 6-H, 7-H); 5,16 (1H, t, 1-H); 4,62 (2H, s, OCH_2CO); 4,16 (1H, m, 5-H); 2,64 ... 2,87 (2H, m, 8-H)
XVIa	7,30 (1H, d, =CH); 5,70 (2H, m, 7-H, 6-H); 5,10 (1H, t, 1-H); 4,11 (2H, t, OCH_2); 4,07 (1H, m, 5-H); 2,80 (1H, m, 8-H); 2,67 (1H, m, 8-H); 2,52 (2H, t, CH_2CO); 2,07 (2H, q, $CH_2CH_2CH_2CO$)
XVIIa	7,27 (1H, d, =CH); 5,70 (2H, m, 6-H, 7-H); 5,10 (1H, t, 1-H); 4,07 (3H, m, 5-H, O—CH_2); 2,64 ... 2,85 (2H, m, 8-H); 2,43 (2H, t, CH_2CO); 1,75 (4H, m, $(CH_2)_2$)

lactone (I) remained. The α-allyllactone (VIII) was isolated with a 60% yield; with the iodoacetic esters the reaction gave yields of only 31-37%, while with iodobutyric and iodovaleric esters the reaction did not go at all.

According to TLC, HPLC, and PMR spectra, the alkylation of the γ-lactone by alkyl iodides and iodoacetic esters takes place stereoselectively. In the case of the reaction of the lactone with allyl bromide, however, two isomers were formed in a ratio of 75:25 (according to the PMR spectra), and they could not be separated by chromatography. As follows from the PMR spectrum of the obtained product (VIII), the spin—spin coupling constants for the 5-H proton ($^3J_{5,6}$, $^3J_{5,1}$, $^4J_{5,7}$, $^3J_{5,4}$) are 1.9, 5.3, 1.9, and 9.4 Hz respectively for the isomer formed in the smaller amount and 1.9, 5.9, 1.9, and 1.9 Hz for the predominant second isomer. The $^3J_{5,4}$ spin—spin coupling constant of 9.4 Hz must in our opinion be attributed to the cis arrangement of the 5-H and 4-H protons, while the $^3J_{5,4}$ value of 1.9 Hz indicates a trans arrangement. Consequently, the isomer formed in the largest amount must have the allyl group at the exo position. The $^3J_{5,4}$ value for compounds (III-VII) amounts on the average to 2 Hz, which indicates the exclusive formation of the exo isomer.

In the reaction with allyl bromide the formation of a small amount of the 4-geminal product (IX) (7.3%) was also detected. The PMR spectrum of this compound does not contain a signal for the 4-H proton but contains signals for the —CH_2

TABLE 3. Mass Spectra of the Synthesized Compounds (III-VIII, X-XII, XIV-XVII)

Compound	m/z (I, %)
III	138 (22) $[M]^{+\cdot}$, 110 (18) $[M-CO]^{+\cdot}$, 109 (52) $[M-COH]^{+}$, 83 (22) $[M-COCHCH_2]^{+}$, 81 (64) $[M-COCH_2CH_3]^{+}$, 79 (100), 77 (28), 56 (70), 41 (28), 39 (38)
IV	152 (2) $[M]^{+\cdot}$, 134 (4) $[M-H_2O]^{+\cdot}$, 124 (100) $[M-C_2H_4]^{+\cdot}$, 95 (67) $[M-C_3H_8]^{+}$:, 124 (80) $[M-C_4H_8]^{+}$:, 93 (18), 80 (24), 79 (100), 67 (22), 55 (27), 41 (27), 39 (20)
V	180 (1) $[M]^{+\cdot}$, 162 (3) $[M-H_2O]^{+\cdot}$, 151 (3) $[M-C_2H_5]^{+}$, 136 (13) $[M-C_3H_8]^{+\cdot}$, 124 (80) $[M-C_4H_8]^{+\cdot}$, 93 (18), 80 (24), 79 (100), 67 (22), 55 (27), 41 (27), 39 (20)
VI	196 (3) $[M]^{+}$; 178 (14) $[M-H_2O]^{+\cdot}$, 165 (10) $[M-OCH_3]^{+}$, 150 (100) $[M-H_2O-CO]^{+\cdot}$, 136 (29) $[M-HCOOCH_3]^{+\cdot}$, 135 (50), 118 (43) $[M-H_2O-HCOOCH_3]^{+\cdot}$, 114 (28), 93 (43), 92 (47), 91 (67), 90 (33), 79 (65), 78 (38), 77 (52), 67 (22), 66 (26), 55 (76), 41 (29), 39 (43)
VII	192 (25) $[M-H_2O]^{+\cdot}$, 165 (38) $[M-OC_2H_5]^{+}$, 164 (100) $[M-C_2H_5OH]^{+\cdot}$, 137 (38) $[M-COOC_2H_5]^{+}$, 136 (60), $[M-HCOOC_2H_5]^{+\cdot}$, 118 (50) $[M-H_2O-HCOOC_2H_5]^{+\cdot}$, 93 (25), 92 (53), 91 (58)
VIII	164 (7) $[M]^{+\cdot}$, 136 (7) $[M-CO]^{+}$, 135 (5), 123 (19) $[M-CH_2CH=CH_2]^{+}$, 120 (19) $[M-CO_2]^{+\cdot}$, 119 (17), 105 (36), 91 (38), 79 (45), 66 (100)
X a	256 (1) $[M]^{+\cdot}$, 238 (3) $[M-H_2O]^{+\cdot}$, 190 (10) $[OCOCHCH(OH)CH=CHC_6H_5]^{+\cdot}$, 172 (5) $(OCOC=CHCH=CHC_6H_5]^{+\cdot}$, 133 (100) $[(HO)CHCH=CHC_6H_5]^{+}$
XI a	298 (8) $[M]^{+\cdot}$, 255 (53) $[M-COCH_3]^{+}$, 238 (7) $[M-CH_3COOH]^{+}$:, 232 (3) $[OCOCHCH(OCOCH_3)CH=CHC_6H_5]^{+\cdot}$, 190 (18) $[OCOCHCH(OH)CH=CHC_6H_5]^{+\cdot}$, 133 (67) $[HOCHCH=CHC_6H_5]^{+}$, 43 (100) $[COCH_3]^{+}$
XI b	298 (7) $[M]^{+\cdot}$, 255 (75), 238 (6), 232 (4), 190 (23), 133 (100), 43 (73)
XII a	238 (100), $[M]^{+\cdot}$, 193 (77) $[M-COOH]^{+}$, 179 (31), 178 (46), 172 (34) $[OCOC=CHCH=CHC_6H_5]^{+\cdot}$, 165 (57), 115 (65)
XII b	238 (100), 193 (64), 179 (28), 178 (39), 172 (25), 165 (53), 115 (64)
XIV	152 (88) $[M]^{+\cdot}$, 134 (100) $[M-H_2O]^{+\cdot}$, 124 (81) $[M-CO]^{+}$:, 123 (46) $[M-HCO]^{+}$, 108 (73) $[M-CO_2]^{+\cdot}$, 107 (31), 106 (54) $[M-H_2O-CO]^{+\cdot}$, 105 (69), 95 (77), 79 (>100)
XV	238 (57) $[M]^{+\cdot}$, 220 (31) $[M-H_2O]^{+\cdot}$, 209 (52) $[M-C_2H_5]^{+}$, 165 (100) $[M-COOC_2H_5]^{+}$, 164 (12), 163 (21), 151 (67) $[M-CH_2COOC_2H_5]^{+}$, 147 (24), 135 (62) $[M-OCH_2COOC_2H_5]^{+}$, 134 (60), 123 (40), 95 (52), 91 (24), 79 (21), 77 (38), 67 (24), 66 (24), 65 (28)
XVI	252 (2) $[M]^{+\cdot}$, 221 (5) $[M-OCH_3]^{+}$, 192 (7) $[M-HCOOCH_3]^{+\cdot}$, 177 (60) $[M-OCH_3-CO_2]^{+}$, 151 (100) $[M-(CH_2)_3COOCH_3]^{+}$, 136 (70), 135 (85) $[M-O(CH_2)_3COOCH_3]^{+}$, 123 (55), 107 (70), 106 (70), 105 (95), 101 (>100) $[(CH_2)_3COOCH_3]^{+}$
XVII	235 (1) $[M-OC_2H_5]^{+}$, 189 (1), 165 (1) $[M-(CH_2)_3COOC_2H_5]^{+}$, 151 (16) $[M-(CH_2)_4COOC_2H_5]^{+}$, 135 (3) $[M-O(CH_2)_4COOC_2H_5]^{+}$, 134 (7), 129 (98) $[(CH_2)_4COOC_2H_5]^{+}$, 101 (100) $[(CH_2)_2COOC_2H_5]^{+}$, 95 (5), 91 (5), 83 (51)
XV a	211 (100) $[M+1]^{+}$, 193 (12) $[M-OH]^{+}$, 180 (9), 135 (50) $[M-OCH_2COOH]^{+}$, 91 (35)
XVI a	239 (32) $[M+1]^{+}$, 221 (4) $[M-OH]^{+}$, 135 (100) $[M-O(CH_2)_3COOH]^{+}$
XVII a	253 (16) $[M+1]^{+}$, 153 (100) $[M-CH(CH_2)_3COOH]^{+}$, 135 (52) $[M-O(CH_2)_4COOH]^{+}$

protons of two different allyl groups in the form of doublets at 2.38 ppm for one substituent and in the form of nonequivalent signals (a doublet of doublets at 2.31 ppm and 2.54 ppm) for the second allyl group (Table 2).

The mass spectra of the obtained compounds [except (VII)] contain molecular ion peaks. Their fragmentation is typical of molecules in which the positive charge is localized in a lactone ring (Table 3). The IR spectra of compounds (III-V, VIII) contain an absorption band at 1765-1770 cm^{-1} characteristic of the carbonyl group of the γ-lactone, and for compounds (VI) and (VII) they also contain a band at 1740 cm^{-1}, corresponding to the ester group, in addition to this band (Table 1).

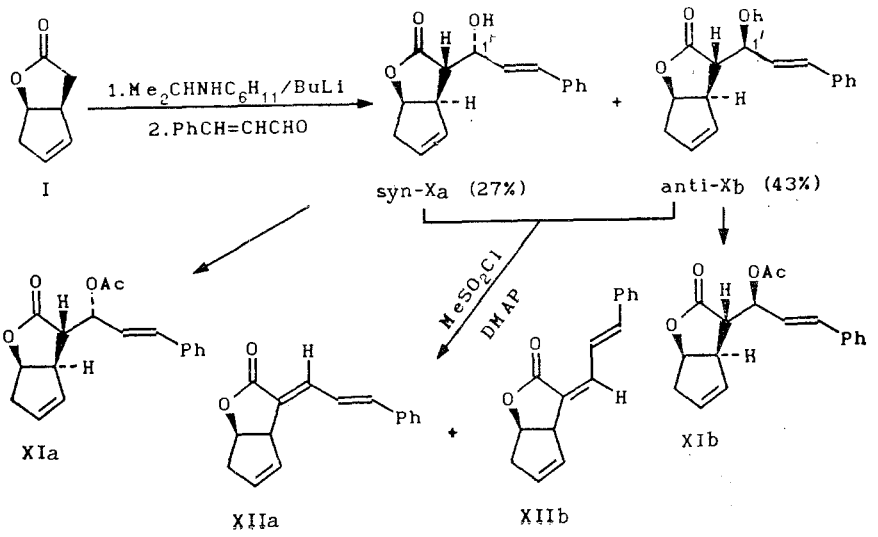
The reaction of γ-lactones with aldehydes in the presence of bases has been insufficiently investigated, in contrast to the reactions of ketones. The literature contains little information on the process itself, the stability of the obtained aldols, and the methods of dehydration [14-16].

Our first investigations included the reaction of the lactone (I) with cinnamaldehyde (scheme 2).

The β-hydroxylactone (X) was obtained as a result of the addition of the carbanion of the lactone (I), formed in the presence of lithium isopropylcyclohexylamide, to cinnamaldehyde in THF at −70°C. Here two crystalline compounds were isolated, i.e., the less polar syn isomer (Xa) with a yield of 27% and the anti isomer (Xb) with a yield of 43%.

The mass spectra of the obtained compounds were identical. They contained the molecular peak and the $[M - H_2O]^{+}$ fragment. In addition, to judge from these spectra, the conjugated system, an element of which is a benzene ring, weakens the bond of the lactone ring, and this radically changes the fragmentation of the compounds compared with the compounds described above. In addition to the molecular ion and the $[M - H_2O]^{+\cdot}$ fragment, the spectrum contains ions of aromatic

Scheme 2



character, corresponding to m/z 190 $[OCOCHCH(OH)CH{=}CHC_6H_5]^+$, 172 $[OCOC{=}CHCH{=}CHC_6H_5]^{+\cdot}$, and also the strongest ion 133 $[(OH)CHCH{=}CHC_6H_5]^+$ (see Table 3).

The PMR spectra of the isomers (X) differ in the chemical shifts of the 4-H [in (Xa) 2.56 and in (Xb) 2.75 ppm] and, more importantly, 1′-H protons [in (Xa) 4.90 and in (Xb) 4.64 ppm] (Table 2). The upfield shift of the 1′-H signal in the case of the isomer (Xb) may indicate that it is distant from the carbonyl group (the anti form) [17]. The small $^3J_{5,4}$ value of 3 Hz indicates that the substituent at the $C_{(4)}$ atom, as in the case of compounds (III-VIII), has the exo orientation in relation to the bicycle.

Dehydration could be expected during the acetylation of the β-hydroxylactones (Xa, b) with acetic anhydride in the presence of dimethylaminopyridine, as in the case of many β-hydroxy ketones [18, 19]. Under the given conditions, however, the acetyl derivatives proved stable. Acetylation was conducted with each isomer in isolation, and compound (XIb) was crystalline while compound (XIa) was an oily substance.

Aldol dehydration takes place through mesylation of the β-hydroxylactone (Xa) in methylene chloride in the presence of dimethylaminopyridine. After only 30 min the reaction was complete. After column chromatography we isolated two isomers, i.e., the less polar crystalline compound (XIIa) with a 29% yield and a second also crystalline isomer (XIIb) with a 39% yield. The analogous compounds were isolated from the anti form of the β-hydroxylactone (Xb), i.e., 13% of the product (XIIa) and 50% of the more polar compound (XIIb).

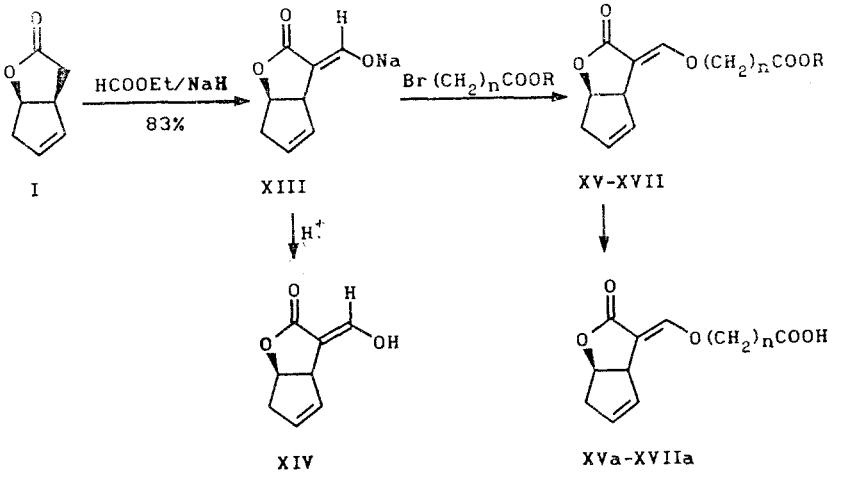
The β-elimination of compounds (Xa) and (Xb) probably takes place through the formation of partly planar carbocations, which adopt the most stable conformation in each of these cases. This gives rise to the different stereoselectivity of the reaction and to the different proportions of the exo-olefin products during the dehydration of compounds (Xa) or (Xb).

The mass spectra of compounds (XIIa, b) are identical and are characterized by molecular ion peaks and by ions of aromatic nature (Table 3). In the PMR spectra of the compounds there is a signal for 1′-H at 8.20 ppm in compound (XIIa) and 7.22 ppm in compound (XIIb). This indicates the presence of a trans-trans-diene system in the less polar compound (XIIa) and a cis-trans-diene system in (XIIb), which is consistent with published data [16, 20]. In the IR spectrum of compounds (XIIa, b) there are strong absorption bands for the exocyclic double bond at 1650 cm^{-1} and the conjugated lactone carbonyl at 1745 cm^{-1}.

The reaction of the γ-lactone with ethyl formate was conducted in the presence of sodium hydroxide by the method in [5]. Instead of diethyl ether we used benzene, since the reaction takes place significantly more quickly and a friable yellowish precipitate of the sodium salt of the hydroxymethylenelactone (XIII) is formed (scheme 4). The PMR spectrum of an aqueous solution of the salts indicates the E configuration for the exocyclic double bond ($\delta_{=CH}$ 8.48 ppm). When the sodium salt of the hydroxymethylenelactone is acidified, the α-hydroxymethylenelactone (XIV) is formed, and its PMR spectrum indicates the presence of Z and E isomers in a ratio of 1:1. The chemical shift at 8.30 ppm corresponds to the trans form, while that at 7.10 ppm corresponds to the cis form of the hydroxymethylenelactone, and this agrees with [10].

The sodium salt of the hydroxymethylenelactone was alkylated by the esters of ω-bromoalkyl acids in THF in the presence of 1 eq of hexamethylphosphorotriamide. The yield of the hydroxymethylene derivative (XV) was 63%. With the esters of longer ω-bromoalkyl acids the yields are reduced (Table 1).

The data from TLC, HPLC, and PMR spectra indicate that compounds (XV-XVII) exist in the E form. In addition to all the signals characteristic of the initial lactone, the PMR spectra of these compounds contain a doublet at 7.16 ppm ($^4J_{5,1'}$ = 2.5 Hz) in compound (XV) and at 7.25 ppm ($^4J_{5,1'}$ = 2.5 Hz) in compounds (XVI, XVII), corresponding to the vinyl proton. According to published data [7, 21], these values of the chemical shifts can be attributed to the E stereochemistry of the oxygen-containing groups of the exocyclic double bond. The presence of the OCH_2CO group in compound (XV) is confirmed by the appearance of singlet at 4.44 ppm, while the two methylene protons in the OCH_2 group in compounds (XVI, XVII) are observed in the form of triplets at 4.05-4.01 ppm. The methylene protons adjacent to the carboxyl group appear as a triplet at 2.36 for (XVII) and 2.45 ppm for (XVI) (Table 2).



XV R=C_2H_5, n=1; XVI R=CH_3, n=3; XVII R=C_2H_5, n=4

The identical configuration of the substituents at the exocyclic double bond in compounds (XIII, XV-XVII) indicates that the negative charge in the ion (XIII) is localized at the "formyl" oxygen atom.

The mass spectra of compounds (XV-XVII) contain molecular ions. As in compounds (III-VIII), localization of the positive charge in the lactone ring is observed, and this shows up in the similar fragmentation of all these compounds. At the same time localization of the positive charge at the ester group of the side chain is possible, as shown by the appearance of ions with m/z 101 and 129. The IR spectra of these compounds contain strong absorption bands for the exomethylene group at 1680 cm^{-1} and for the carbonyl groups of the lactone and ester at 1740 cm^{-1}.

The corresponding acids (XVa-XVIIa) were obtained from compounds (XV-XVII) by the action of lithium hydroxide in a 1:1 mixture of THF and water. By TLC it is possible to observe how cleavage of the lactone ring occurs simultaneously with hydrolysis of the ester group, but recyclization occurs during isolation of the acid after acidification of the reaction mixture. The acid (XVa) is a crystalline compound and is formed in the first 5-10 min. The longer the side chain of the initial ester (XVI, XVII), the longer the hydrolysis takes. Thus, the ester (XVI) was fully hydrolyzed under analogous conditions after 20 h, and the corresponding acid was isolated with a yield of 60%, while in the case of compound (XVII) 22% of the initial ester remained after 20 h with an acid yield of 57%.

The mass spectra of the acids (FAB) contain molecular ions and the $[M - O(CH_2)_nCOOH]^+$ fragment (Table 3). The IR spectra contain strong absorption bands at 1770, 1715, and 1660 cm^{-1}, corresponding to the lactone carbonyl, the carboxyl group, and the exomethylene double bond. The PMR spectra of compounds (XVa-XVIIIa) do not contain signals for the ester group. In the spectrum of compound (XVa) the 1′-H chemical shift moves downfield by 0.25 ppm compared with the corresponding ester. In other respects the spectra of the acids do not differ from the spectra of their esters (Table 2).

EXPERIMENTAL

The PMR spectra were obtained on a Bruker WM 360 spectrometer in deuterochloroform with TMS as internal standard. The mass spectra were recorded at 70 eV on a Kratos MS 50 mass spectrometer. The FAB mass spectra were recorded on the same Kratos WM-50 instrument fitted with an FAB 11 NF source (Ion Tech Ltd.) with argon as ionizing gas and thioglycerol as matrix. The IR spectra were recorded on a Perkin-Elmer 580B spectrometer in chloroform solution or in Nujol.

For the chromatographic investigations we used a Laboratorni Pristroje liquid chromatograph (Prague) with a differential refractometer as detector. In normal-phase HPLC we used a column (3.0 × 150 mm) filled with Separon SGX with a particle size of 5 μ. The capacity coefficients of the compounds were calculated by means of the equation $K = (t_R - t_0)/t_0$, where t_R is the retention time of the sorbate and t_0 is the retention time of hexane. The employed solvent systems are given in Table 1.

All the reactions were conducted in an argon atmosphere. After extraction the organic solutions were dried with sodium sulfate and evaporated under vacuum at a temperature not higher than 40°C. The reaction was monitored by TLC on Silufol UV-254 plates. The spots of the substances were detected in UV light and by spraying the plates with a 10% solution of phosphomolybdic acid in ethanol followed by heating at 120°C. For purification we used column chromatography on Silasorb 600 (Lachema, Czech).

4-Methyl-2-oxabicyclo[3.3.0]-6-octen-3-one (III) ($C_8H_{10}O_2$). Lithium diisopropylamide was prepared from 0.13 g (1.3 mmole) of diisopropylamine and 0.47 ml (1.1 mmole) of a 2.35 N hexane solution of butyllithium in 1.4 ml of THF at −70°C with stirring for 15 min. To the obtained solution of lithium diisopropylamide over 1 h we added dropwise 0.11 g (0.9 mmole) of the γ-lactone (I) in 1 ml of THF while keeping the temperature at −70°C. The mixture was stirred for a further 15 min, and 0.16 g (1.1 mmole) of methyl iodide in 1 ml of THF, containing 0.18 g (1.1 mmole) of HMPTA, was then added drop by drop. The temperature was slowly raised to −40°C, and the mixture was kept at this temperature for 3 h and then left at −18°C overnight. The reaction mixture was treated with 50 ml of a saturated solution of ammonium chloride and extracted with chloroform (5 × 20 ml). The crude product was purified on Silasorb with system A as eluant. We obtained 0.054 g (42%) of compound (III) (R_f 0.44) and 0.05 g (45%) of the initial lactone (R_f 0.23) (system A).

Compounds (IV-VII) were obtained similarly.

4-Allyl-2-oxabicyclo[3.3.0]-6-octen-3-one (VIII) ($C_{10}H_{12}O_2$). To a solution of 0.77 g (4.2 mmole) of sodium bistrimethylsilylamide in 0.3 ml of THF at −70°C we added slowly with stirring 0.17 g (1.4 mmole) of the γ-lactone (I) in 1.5 ml of THF. After 20 min we slowly added 0.68 g (5.6 mmole) of allyl bromide in 0.5 ml of THF containing 0.76 g (4.2 mmole) of HMPTA. The mixture was kept at −70°C for 1 h, the temperature was raised to −40°C, and the mixture was stirred for a further 4 h. The mixture was diluted twice with water and extracted with ether. The crude product was purified by chromatography on Silasorb with systems G, F, and E successively as eluants. We obtained 0.02 g (73%) of α-gem-allyllactone (IX) (R_f 0.69), 0.14 g (60%) of α-allyllactone (VIII) (R_f 0.58), and 0.019 g (11%) of the lactone (I) (R_f 0.33) (system E).

4-(1-Hydroxy-3-phenyl-2-propenyl)-2-oxabicyclo[3.3.0]octen-3-one (X) ($C_{16}H_{16}O_3$). To 1.32 ml (7.9 mmole) of isopropylcyclohexylamine in 2 ml of THF at 0 to −5°C we added dropwise 3 ml (7 mmole) of a 2.35 N hexane solution of butyllithium. After 15-20 min the mixture was cooled to −78°C, and 0.3 g (2.4 mmole) of the γ-lactone (I) in 2 ml of THF was added over 15 min. After 30 min 0.57 ml (4.8 mmole) of cinnamaldehyde in 2 ml of THF was added. After 1 h the mixture was diluted with ether, and the organic layer was washed with water and saturated sodium chloride solution, dried, and evaporated. The residue was chromatographed on Silasorb with a 3:1 mixture of hexane and dioxane as eluant. The obtained fraction, containing a mixture of the isomers (X), was chromatographed once more with system E as eluant. We obtained 0.16 g (27%) of the isomer (Xa) (mp 119-120°C) and 0.26 g (43%) of the isomer (Xb) (mp 62-63.5°C, from a mixture of hexane and ethyl acetate).

4-(1-Acetoxy-3-phenyl-2-propenyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (XI) ($C_{18}H_{18}O_4$). To 0.04 g (0.2 mmole) of the aldol (Xa) in 1 ml of methylene chloride we added 0.02 g (0.2 mmole) of dimethylaminopyridine and 32 μl (0.3 mmole) of acetic anhydride. After 30 min the mixture was diluted with methylene chloride, washed with water and saturated sodium chloride solution, dried, and evaporated. We obtained 0.05 g (99%) of the oily substance (XIa).

The acetal derivative (XIb) was obtained similarly in the form of a crystalline compound melting at 131.5-132.5°C.

4-(3-Phenylpropenylidene)-2-oxabicyclo[3.3.0]-6-octen-3-one (XII) ($C_{16}H_{14}O_2$). To 0.08 g (0.32 mmole) of the isomer (Xa) in 6 ml of methylene chloride we added with stirring 0.2 g (1.6 mmole) of dimethylaminopyridine and 0.06 ml

(0.8 mmole) of methanesulfonyl chloride. After 1 h 30 min the mixture was diluted with methylene chloride, washed with water and saturated sodium chloride solution, dried, and evaporated. The residue was chromatographed on Silasorb with system F as eluant. We obtained 0.022 g (29%) of compound (XIIa) (mp 121-123°C) and 0.03 g (39%) of compound (XIIb) (mp 99-100°C, from a mixture of hexane and ethyl acetate).

Compounds (XIIa) (yield 13%) and **(XIIb)** (yield 50%) were obtained similarly from the aldol (Xb).

4-Hydroxymethylene-2-oxabicyclo[3.3.0]-6-octen-3-one (XIV) ($C_8H_8O_3$). To a suspension of 0.12 g (3.5 mmole) of sodium hydride and 8 ml of benzene, while stirring, we added over 30-40 min 0.26 g (2.1 mmole) of the lactone (I) in 4 ml of benzene and 0.6 ml (7.1 mmole) of ethyl formate. We immediately added one drop of ethanol so that the solution boiled gently and continued to stir the mixture at room temperature. After 2 h the reaction mixture was diluted three times with dry ether. The obtained crystals were filtered off, washed on the filter with ether, and dried under vacuum. We obtained 0.3 g (83%) of the yellowish powder of the sodium salt of hydroxymethylenelactone (XIII). The latter was suspended in 20 ml of ethyl acetate and cooled to −20°C, and 2 M hydrochloric acid was added with stirring to dissolve the salt. The organic solution was separated, washed with water and saturated sodium chloride solution, dried, and evaporated. After chromatographic purification on Silasorb in systems E and then C we obtained 0.23 g (87%) of compound (XIV) melting at 110.5-112.5°C.

4-(Ethoxycarbonylmethoxymethylene)-2-oxabicyclo[3.3.0]-6-octen-3-one (XV) ($C_{12}H_{14}O_5$). A solution of 0.29 g (1.7 mmole) of the sodium salt of the hydroxymethylenelactone (XIII) in 4 ml of THF, containing 2 ml of HMPTA, was cooled to −20°C, and 0.56 ml (5.0 mmole) of ethyl bromoacetate and 2 ml of THF was added with stirring over 15-30 min. The mixture was stirred at this temperature for 1 h, the temperature was raised to room temperature, and the mixture was stirred by a further 2 h. The mixture was then diluted with 50 ml of water, the solution was neutralized with 2% hydrochloric acid, and the product was extracted with ether. The crude product was purified by chromatography on Silasorb with gradient elution with hexane in ethyl acetate from 3:1 to 1:1. We obtained 0.25 g (63.7%) of the crystalline product (XV); R_f 0.47 (system D), mp 102.5-103°C.

Compounds (XVI) and (XVII) were obtained similarly.

4-(Carboxymethoxymethylene)-2-oxabicyclo[3.3.0]-6-octen-3-one (XVa) ($C_{13}H_{16}O_5$). A solution of 0.19 g (0.8 mmole) of the ester (XV) in 8 ml of a 1:1 mixture of water and tetrahydrofuran was cooled to 0°C, and 1.6 ml (1.6 mmole) of a 1 M solution of lithium hydroxide in water was added with stirring. The reaction was complete after 5-10 min. The mixture was acidified to pH 3 with 2 N hydrochloric acid, the THF was distilled, and the aqueous residue was extracted with ethyl acetate. The organic solution was dried and evaporated, and the residue was chromatographed on Silasorb with a 2:1 mixture of chloroform and ethyl acetate as eluant. We obtained 0.14 g (83%) of the crystalline acid (XVa); R_f 0.31 (2:1 chloroform—ethyl acetate), mp 117-118°C. IR spectrum (Nujol): 1770 (CO); 1715 (COOH); 1660 cm^{-1} (C=CH).

The acids (XVIa) and (XVIIa) were obtained similarly.

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X-RAY EMISSION SPECTROSCOPY AND ELECTRONIC STRUCTURE OF HETEROCYCLIC COMPOUNDS. 1. FURAN

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The electronic structure of the furan molecule was investigated by x-ray spectroscopy. A quantum-chemical calculation (ab initio) was undertaken, and the results were compared with the experimental data. The interpretation of the x-ray spectra of the molecule, the carbon atoms of which have a different energy position for the 1s levels, is discussed in detail. The electronic transitions from the MO to these core levels are clearly recorded in the carbon x-ray spectrum. It was shown experimentally that the HOMO is an orbital in which the electron density is localized at the carbon atoms.

The present work begins a cycle of articles devoted to the investigation of a series of heterocyclic compounds by x-ray spectroscopy. The furan molecule has been studied in detail by quantum chemistry and photoelectron spectroscopy (PES) (e.g., see [1-3] and the references in them) and also by x-ray electron spectroscopy (XES) [4, 5]. The investigations have made it possible to obtain a fairly full picture of the electronic structure of furan, i.e., the energy position of the MO and the structure of the wave functions. Since the latter was only established on the basis of theoretical calculations, it was necessary to determine it experimentally. X-ray spectroscopy was used for this purpose. There are no such data in the literature, and the aim of the present work was therefore to investigate the electronic structure of the furan molecule from the standpoint of its x-ray emission spectra.

We obtained the OK_α and CK_α spectra (the x-ray emission spectra of oxygen and carbon respectively for furan) (Fig. 1). The experimental and smoothed spectra were reduced to the single energy scale of ionization potentials using the energy position of the inner O1s and C1s levels,* taken from [4,5]. However, whereas the OK_α spectrum is reduced to a single scale in the usual way, e.g., by the method in [6], for the CK_α spectrum it becomes indeterminate on account of the presence of two types of carbon atoms in the furan molecule (in relation to the oxygen) and, accordingly, two C1s levels. The CK_α spectrum, reduced to the scale of ionization potentials by means of the $C_{3,4}1s$ level, is shown in Fig. 1 by the solid line (the lower scale of electron transition energies, E), while the spectrum obtained by means of the $C_{2,5}1s$ level is represented by the dotted line (the upper scale of transition energies). The photoelectron spectrum (HeI), presented in the same figure was reproduced from [2]. The x-ray spectra were synthesized on the basis of the *ab initio* calculation that we made (Fig. 2). The identification of the intensities of the individual x-ray transitions is given in Fig. 2 and in Table 1.

*The ionization potentials of the C1s orbitals: $I(C_21s) = I(C_51s) = I(C_{2,5}1s)$; $I(C_31s) = I(C_41s) = I(C_{3,4}1s)$.

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