TOTAL SYNTHESIS AND PROPERTIES OF PROSTAGLANDINS

35.* SYNTHESIS AND PROPERTIES OF 4-CARBOMETHOXY-ALKYLAMINOMETHYLENE-(+)2-OXABICYCLO[3.3.0]-6-OCTEN-3-ONES

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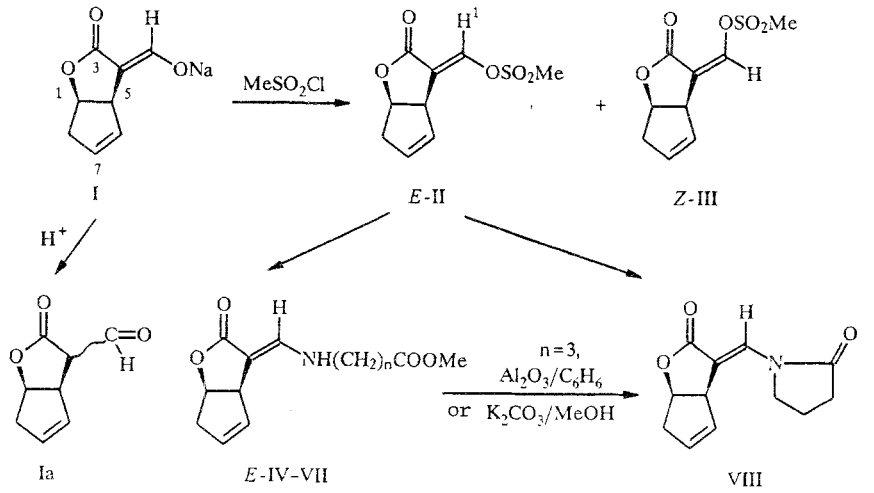
Reaction of (+)4-mesyloxymethylene-2-oxabicyclo[3.3.0]-6-octen-3-one with ω-amino acids of different lengths gave (+)4-carbomethoxyalkylaminomethylene-2-oxabicyclo[3.3.0]-6-octen-3-ones. For the γ-aminobutyric ester, the corresponding aminomethylene derivative was obtained both in the linear and the cyclic forms. Acylations of the synthesized enamino lactones by acetyl and benzoyl chlorides were investigated.

In a preceding publication [2], we reported the functionalization of 2-oxabicyclo[3.3.0]-6-octen-3-one (hereafter the γ-lactone) in the α-position to the carbonyl group and included preparation of the carboxyalkyloxymethylene derivatives. Using the sodium salt of α-formyl-γ-lactone I [2] as starting material we also obtained the carbomethoxyalkylaminomethylene derivatives IV-VII according to the scheme:



The mesyloxymethylene γ-lactones II and III were the reaction intermediates. Depending on the conditions for acylating hydromethylene lactone I there were obtained only the trans-mesylate (in aqueous acetone) or a mixture of the trans- and cis-isomers II, III in the ratio 2:1 (in anhydrous ether). These were readily separated by column chromatography on silasorb, both isomers being crystalline materials (Table 1). In their PMR spectra, the most marked differences were seen in the chemical shifts

*For Communication 34 see [1].

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TABLE 1. Physical Parameters for II-VIII

Compound	Mp, °C	$[\alpha]_D^{20}$ (c = 1, $CHCl_3$)	Mobility		Yield, %
			R_f (system)*	K (system)*	
II	63...64	+260	0,57 (B)	2,9 (A)	98
III	77...78	+235	0,42 (B)	4,8 (A)	31
IV	125...126	+294	0,45 (E)	4,2 (D)	63 (71)**
V	87...88	+331	0,45 (E)	4,8 (D)	52 (67)
VI	58...59	+334	0,49 (E)	5,1 (D)	57
VII	73...74	+303	0,54 (E)	4,9 (D)	51 (61)
VIII	182...183	+356	0,34 (E)	8,0 (D)	56

*Solvent systems: hexane–ethylacetate, 1.5:1 (A); 1:1 (B); 1:2 (C); hexane–ethylacetate–dioxane, 9:10:1 (D); chloroform–ethylacetate, 1:4 (E).

**Product yields obtained at the solvent boiling point.

of the 1′-H vinyl proton [δ = 7.65 ppm for E(II) and 7.05 ppm for the Z-form III (Table 2)]. The mass and IR spectra were almost identical (Table 3).

The trans-mesylate II was then treated with the ω-amino acid methyl ester in methanol with K_2CO_3. The nucleophilic substitution proceeds slowly. The longer the ω-amino acid the more slowly it proceeds. At room temperature the reaction with glycine methyl ester is complete within 21 h whereas that with ω-aminovalerate ester takes 66 h. At reflux (60°C) the reaction times are 6 and 18 h, respectively. At room temperature there remains 2-7% of unreacted mesylate II, and the α-formyl lactone Ia, with 51-63% yields of the target compounds IV-VII. At higher temperature the yields of the latter are slightly increased (61-71%) but formation of the side products does not occur (see Table 1).

All of the compounds IV-VII are crystalline. Their melting points are markedly decreased with lengthening of the side chain from n = 1 (IV) to n = 3 (VI), but in the case of VII (n = 4) it is increased.

An increased chromatographic mobility (TLC) was observed for the third member of the amine series (VI, n = 3). A linear rise for a further increase in the number of methylene groups is to be expected since we had observed this in a series of amides containing a similar fragment [3].

According to PMR data, compounds IV-VII occur in the E-form. The vinyl proton is observed as a double doublet at 7.10-7.15 ppm (see Table 2).

The Z-mesylate III was used as starting material in order to prepare the Z-isomer of IV. However, the E-form of the required product was obtained with a small admixture of the Z-isomer. In the PMR spectrum there were signals at 7.10 ppm for the vinyl proton and 3.90 ppm for the 5-H proton in the E-isomer of IV and a double doublet at 6.52 ppm for the vinyl proton and a multiplet at 3.85 ppm for 5-H, these being characteristic of the Z-form [4, 5]. In addition, in the case of the cis-isomer the protons H^7 and H^6 are nonequivalent and their signals occur at 5.60 and 5.50 ppm, respectively. We could not increase the yield of the cis-product of IV by changing the reaction conditions (substituting K_2CO_3 by CH_3COONa, Cs_2CO_3, NaF, t-BuOK, or methanol by THF). As shown in a control experiment, the cis-methylate III is fully converted in one hour to the trans-form under the conditions for obtaining the α-aminomethylene derivatives of the γ-lactone.

A characteristic feature of the mass spectra of IV-VII is the presence of the molecular ions and highest intensity peaks for the fragments $[M-(CH_2)_{n-1}COOCH_3]^+$ (see Table 3).

The course of the reaction of mesylate II with methyl γ-aminobutyrate depends significantly on the ratio of the latter and K_2CO_3. Compound VI is obtained if these reagents occur in the ratio 1:1 or with an excess of γ-aminobutyric acid (1:0.8). If the K_2CO_3 is in excess (1:1.35 to 1:2), an intramolecular cyclization of the product VI occurs. The product is the cyclic compound VIII (see Scheme 1). The latter was also obtained by us when the α-aminomethylene-γ-lactone VI was held in MeOH in the presence of K_2CO_3 or when refluxing for 3 h with Al_2O_3 in benzene or methylene chloride. From TLC and HPLC, the chromatographic mobility of this compound is significantly less than that of the linear analog VI (see Table 1).

The PMR spectra of VI and VIII are quite different. The spectrum of VIII shows no signals for the ester or –NH protons. The vinyl proton appears at lower field (7.86 ppm) as a doublet and low field shifts are also seen for the protons at

TABLE 2. Spectra of the Synthesized Compounds II-XVI

Compound	Chemical shift, δ, ppm
II	7,65 (1H, d, =CH); 5,77 (1H, m, 7-H); 5,62 (1H, m, 6-H); 5,16 (1H, m, 1-H); 4,16 (1H, m, 5-H); 3,23 (3H, s, OSO_2CH_3); 2,62....2,88 (2H, m, 8-H)
III	7,05 (1H, d, =CH); 5,80 (1H, m, 7-H); 5,51 (1H, m, 6-H); 5,14 (1H, m, 1-H); 4,06 (1H, m, 5-H); 3,23 (3H, s, OSO_2CH_3); 2,62...2,88 (2H, m, 8-H)
IV	7,10 (1H, d.d, =CH); 5,75 (2H, m, 7-H, 6-H); 5,08 (1H, t, 1-H); 4,70 (1H, m, NH); 4,00 (2H, d, N—CH_2); 3,95 (1H, m, 5-H); 3,70 (3H, s, $COOCH_3$); 2,64...2,85 (2H, m, 8-H)
V	7,13 (1H, d.d. =CH); 5,72 (2H, m, 7-H, 6-H); 5,06 (1H, t, 1-H); 5,02 (1H, m, NH); 3,89 (1H, m, 5-H); 3,70 (3H, s, $COOCH_3$); 3,35 (2H, q, N—CH_2); 2,40...2,75 (4H, 8-H, CH_2CO)
VI	7,10 (1H, d.d. =CH); 5,70 (2H, m, 7-H, 6-H); 5,02 (1H, m, 1-H); 4,67 (1H, m, NH); 3,88 (1H, m, 5-H); 3,69 (3H, c, $COOCH_3$); 3,25 (2H, q, N—CH_2); 2,68 (2H, m, 8-H); 2,38 (2H, m, CH_2CO); 1,90 (2H, qb, $CH_2\underline{CH_2}CH_2$)
VII	7,15 (1H, d.d. =CH); 5,70 (2H, m, 7-H, 6-H); 5,02 (1H, m, 1-H); 4,67 (1H, m, NH); 3,85 (1H, m, 5-H); 3,69 (3H, c, $COOCH_3$); 3,18 (2H, q, N—CH_2); 2,68 (2H, m, 8-H); 2,35 (2H, m, CH_2CO); 1,60 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$)
VIII	7,86 (1H, d, =CH); 5,81 (1H, m, 7-H); 5,53 (1H, m, 6-H); 5,08 (1H, t, 1-H); 4,29 (1H, m, 5-H); 3,97 (2H, t, N—CH_2); 2,70...2,86 (2H, m, 8-H); 2,54 (2H, m, CH_2CO); 2,22 (2H, qb, $\underline{CH_2}CH_2CO$)
IX	7,67 (1H, d, =CH); 5,75 (1H, m, 7-H); 5,44 (1H, m, 6-H); 5,00 (1H, m, 1-H); 4,72 (1H, d, N—CH_2); 4,32 (1H, d, N—CH_2); 4,00 (1H, m, 5-H); 3,70 (3H, s, $COOCH_3$); 2,68 (2H, m, 8-H); 2,35 (3H, s, $COCH_3$)
IXa	7,24 (1H, d, =CH); 5,76 (1H, m, 7-H); 5,63 (1H, m, 6-H); 5,09 (1H, m, 1-H); 4,81 (2H, s, N—CH_2); 4,00 (1H, m, 5-H); 3,75 (3H, s, $COOCH_3$); 2,70 (2H, m, 8-H); 2,25 (3H, s, $COCH_3$)
X	7,59 (1H, d, =CH); 5,79 (1H, m, 7-H); 5,58 (1H, m, 6-H); 5,08 (1H, m, 1-H); 4,40 (1H, m, N—CH_2); 4,25 (1H, m, 5-H); 3,90 (1H, m, N—CH_2); 3,66 (3Hs, $COOCH_3$); 2,80 (2H, m, 8-H); 2,62 (2H, t, CH_2CO); 2,35 (3H, s, $COCH_3$)
Xa	6,96 (1H, d, =CH); 5,75 (1H, m, 7-H); 5,52 (1H, m, 6-H); 5,07 (1H, m, 1-H); 4,26 (3H, m, 5-H, N—CH_2); 3,64 (3H, s, $COOCH_3$); 2,75 (2H, m, 8-H); 2,62 (2H, t, CH_2CO); 2,22 (3H, s, $COCH_3$)
XI	7,57 (1H, d, =CH); 5,75 (1H, m, 7-H); 5,48 (1H, m, 6-H); 5,00 (1H, m, 1-H); 4,15 (1H, м, 5-H); 4,10 (1H, м, N—CH_2); 3,57 (3H, c, $COOCH_3$); 3,50 (1H, m, N—CH_2); 2,68 (2H, m, 8-H); 2,29 (3H, s, $COCH_3$); 1,92 (2H, t, CH_2CO); 1,80 (2H, qb, $CH_2\underline{CH_2}CH_2$)
XII	7,61 (1H, d, =CH); 5,79 (1H, m, 7-H); 5,51 (1H, m, 6-H); 5,08 (1H, m, 1-H); 4,10 (1H, m, 5-H); 4,10 (1H, m, N—CH_2); 3,62 (3H, s, $COOCH_3$); 3,40 (1H, m, N—CH_2); 2,77 (2H, m, 8-H); 2,34 (3H, s, $COCH_3$); 2,34 (2H, t, CH_2CO); 1,60 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$)
XIII	7,62 (1H, d, =CH); 7,46 (5H, m, COC_6H_5); 5,80 (1H, m, 7-H); 5,55 (1H, m, 6-H); 5,00 (1H, m, 1-H); 4,88 (1H, d, N—CH_2); 4,60 (1H, d, N—CH_2); 4,08 (1H, m, 5-H); 3,77 (3H, s, $COOCH_3$); 2,74 (2H, 8-H)
XIV	7,49 (1H, d, =CH); 7,42 (5H, m, COC_6H_5); 5,78 (1H, m, 7-H); 5,67 (1H, м, 6-H); 5,05 (1H, m, 1-H); 4,17 (1H, m, 5-H); 3,68...4,61 (2H, m, N—CH_2); 3,67 (3H, $COOCH_3$); 2,71 (4H, m, 8-H, $\underline{CH_2}COOCH_3$)
XIVa	7,42 (5H, m, COC_6H_5); 6,75 (1H, d, =CH); 5,66 (1H, m, 7-H); 5,33 (1H, m, 6-H); 4,95 (1H, m, 1-H); 4,27 (2H, t, N—CH_2); 3,77 (1H, m, 5-H); 3,67 (3H, s, $COOCH_3$); 2,62 (4H, 8-H, $\underline{CH_2}COOCH_3$)
XV	7,46 (1H, d, =CH); 7,37 (5H, m, COC_6H_5); 5,72 (1H, m, 7-H); 5,52 (1H, m, 6-H); 5,00 (1H, m, 1-H); 4,22 (1H, m, N—CH_2); 4,20 (1H, m, 5-H); 3,78 (1H, m, N—CH_2); 3,61 (3H, s, $COOCH_3$); 2,75 (2H, m, 8-H); 2,37 (2H, t, $\underline{CH_2}COOCH_3$); 1,94 (2H, кв, $CH_2\underline{CH_2}CH_2COOCH_3$)
XVa	7,41 (5H, m, COC_6H_5); 6,77 (1H, d, =CH); 5,68 (1H, m, 7-H); 5,35 (1H, m, 6-H); 5,00 (1H, m, 1-H); 3,70...4,25 (3H, m, 5-H, N—CH_2); 3,59 (3H, c, $COOCH_3$); 2,64 (2H, m, 8-H); 2,33 (2H, t, $\underline{CH_2}COOCH_3$); 1,90 (2H, qb, $CH_2\underline{CH_2}CH_2COOCH_3$)
(*E*, *Z*)-XVI	7,56 (0,5H, d, =CH, trans); 7,44 (5H, m, COC_6H_5); 6,77 (0,5H, d, =CH, 5,26...5,93 (2H, м, 7-H, 6-H); 5,06 (1H, m, 1-H); 4,01 (2H, m, N—CH_2); 3,82 (1H, m, 5-H); 3,64 (1,5H, c, $COOCH_3$); 3,62 (1,5H, c, $COOCH_3$); 2,53...2,87 (2H, m, 8-H); 2,16...2,53 (2H, m, $\underline{CH_2}CH_2CH_2COOCH_3$); 1,57...1,79 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}COOCH_3$)

5-H (4.29 ppm), $-CH_2CO-$ (2.54 ppm), and $-CH_2\underline{CH_2}CH_2-$ (2.22 ppm) which point to the cyclic structure. The signal for the $-N-CH_2-$ protons appears as a triplet at 3.97 ppm. Protons H^7 and H^6 are nonequivalent, evidently because of their interaction with the protons of the lactam ring (Table 2).

In mildly acid medium the α-aminomethylene derivatives IV-VII are readily converted to the α-formyl-γ-lactone Ia, which hinders the preparation of the corresponding acids.

TABLE 3. Mass Spectra and IR Spectra of II-XVI

Compound	Mass spectra, m/z, (I_{rel}, %)	IR spectra, ν, cm^{-1}
1	2	3
II	230 (16) $[M]^{+\cdot}$, 201 (3), 152 (33), 151 (83) $[M-SO_2CH_3]^+$, 134 (100), 133 (40), 123 (40), 106 (37), 105 (33)	1765 (CO), 1695 (C=CH)
III	230 (6) $[M]^{+\cdot}$, 201 (4), 152 (31), 151 (60) $[M-SO_2CH_3]^+$, 134 (100), 133 (27), 123 (38), 106 (50), 105 (44)	1770 (CO), 1680 (C=CH)
IV	223 (31) $[M]^{+\cdot}$, 164 (100) $[M-COOCH_3]^+$, 146 (50), 118 (62)	3430 (NH), 1750 (CO), 1735 ($COOCH_3$), 1660 (C=CH)
V	237 (100) $[M]^{+\cdot}$, 219 (4) $[M-H_2O]^{+\cdot}$, 209 (12) $[M-CO]^+$, 206 (6) $[M-OCH_3]^+$, 192 (15), 164 (92) $[M-CH_2COOCH_3]^+$, 146 (31), 118 (50)	3430 (NH), 1730 (CO, $COOCH_3$), 1655 (C=CH)
VI	251 (16) $[M]^{+\cdot}$, 164 (100) $[M-(CH_2)_2COOCH_3]^+$, 146 (47), 118 (39)	3430 (NH), 1730 (CO, $COOCH_3$), 1655 (C=CH)
VII	265 (13) $[M]^{+\cdot}$, 216 (13), 164 (100) $[M-(CH_2)_3COOCH_3]^+$, 149 (14) $[M-(CH_2)_4COOCH_3-H]^+$, 146 (47), 118 (33)	3430 (NH), 1730 (CO, $COOCH_3$), 1655 (C=CH)
VIII	219 (36) $[M]^{+\cdot}$, 202 (100) $[M-OH]^+$, 191 (32) $[M-CO]^+$, 173 (36), 162 (40), 146 (40), 118 (27)	1755 (CO, NCO), 1660 (C=CH)
IX	265 (4) $[M]^{+\cdot}$, 234 (4) $[M-OCH_3]^+$, 223 (76) $[M-COCH_2]^+$, 222 (5) $[M-COCH_3]^+$, 221 (4) $[M-COCH_3-H]^+$, 206 (4) $[M-COOCH_3]^+$, 191 (7) $[M-CH_2COOCH_3-H]^+$, 165 (13), 164 (100) $[M-COCH_2-COOCH_3]^+$, 163 (13), 146 (27), 133 (18), 121 (60), 118 (29), 106 (16), 105 (10)	1755 (CO, $COOCH_3$), 1715 ($COCH_3$), 1655 (C=CH)
IXa	265 (2) $[M]^{+\cdot}$, 234 (3) $[M-OCH_3]^+$, 223 (68) $[M-COCH_2]^+$, 222 (6) $[M-COCH_3]^+$, 221 (6) $[M-COCH_3-H]^+$, 206 (4) $[M-COOCH_3]^+$, 191 (15) $[M-CH_2COOCH_3-H]^+$, 165 (11), 164 (100) $[M-COCH_2-COOCH_3]^+$, 163 (13), 146 (36), 134 (11), 106 (15)	1760 (CO, $COOCH_3$), 1710 ($COCH_3$), 1645 (C=CH)
X	279 (2) $[M]^{+\cdot}$, 251 (2) $[M-CO]^+$, 248 (2) $[M-OCH_3]^+$, 247 (100) $[M-OCH_3-H]^+$, 208 (16) $[M-CO-COCH_3]^+$, 164 (65) $[M-CO-(CH_2)_2COOCH_3]^+$, 146 (21), 132 (21), 118 (30)	1745 (CO, $COOCH_3$), 1705 ($COCH_3$), 1645 (C=CH)
Xa	236 (56) $[M-COCH_3]^+$, 235 (6) $[M-COCH_3-H]^+$, 234 (12), 207 (10), 205 (3) $[M-COCH_3-OCH_3]^+$, 191 (8) $[M-(CH_2)_2COOCH_3-H]^+$, 176 (4), 164 (34), 146 (12), 132 (14), 118 (24), 106 (16), 91 (18), 87 (100)	1745 (CO, $COOCH_3$), 1690 ($COCH_3$), 1640 (C=CH)
XI	293 (4) $[M]^{+\cdot}$, 252 (13), 251 (85) $[M-COCH_2]^+$, 249 (25) $[M-CO_2]^{+\cdot}$, 220 (21) $[M-COCH_2-OCH_3]^+$, 178 (23), 164 (100) $[M-COCH_2-(CH_2)_2COOCH_3]^+$, 149 (48), 146 (30), 118 (30), 101 (38)	1745 (CO, $COOCH_3$), 1705 ($COCH_3$), 1645 (C=CH)
XII	307 (3) $[M]^{+\cdot}$, 279 (6) $[M-CO]^+$, 265 (90) $[M-COCH_2]^+$, 264 (23), 261 (35), 234 (32), 216 (26), 178 (16), 167 (32), 164 (>100) $[M-CO-(CH_2)_4COOCH_3]^+$, 149 (100), 146 (52), 118 (39), 115 (33)	1745 (CO, $COOCH_3$), 1710 ($COCH_3$), 1645 (C=CH)
XIII	327 (12) $[M]^{+\cdot}$, 296 (5) $[M-OCH_3]^+$, 293 (61), 268 (10) $[M-COOCH_3]^+$, 262 (29), 223 (14) $[M-OCH_3-CH_2COOCH_3]^+$, 222 (100) $[M-COC_6H_5]^+$, 199 (31), 162 (22), 152 (46), 134 (>100), 124 (34), 108 (47), 106 (>100), 105 (>100)	1750 (CO, $COOCH_3$), 1695 (COC_6H_5), 1645 (C=CH)
XIV	341 (8) $[M]^{+\cdot}$, 298 (15), 297 (100) $[M-CO_2]^{+\cdot}$, 276 (38), 238 (38) $[M-CO_2-COOCH_3]^+$, 236 (46) $[M-COC_6H_5]^+$, 210 (30), 204 (15), 106 (92), 105 (>100)	1740 (CO, $COOCH_3$), 1690 (COC_6H_5), 1640 (C=CH)
XV	355 (6) $[M]^{+\cdot}$, 312 (19), 311 (63) $[M-CO_2]^{+\cdot}$, 290 (19), 250 (44) $[M-COC_6H_5]^+$, 218 (19), 167 (38), 149 (100) $[M-COC_6H_5-(CH_2)_3COOCH_3]^+$, 106 (60), 105 (>100)	1745 (CO, $COOCH_3$), 1685 (COC_6H_5), 1640 (C=CH)
XVa	355 (3) $[M]^{+\cdot}$, 312 (13), 311 (50) $[M-CO_2]^{+\cdot}$, 290 (15), 250 (35) $[M-COC_6H_5]^+$, 218 (10), 167 (33), 149 (100) $[M-COC_6H_5-(CH_2)_3COOCH_3]^+$, 106 (60), 105 (>100)	1745 (CO, $COOCH_3$), 1680 (COC_6H_5), 1635 (C=CH)
(*E*, *Z*)-XVI	369 (11) $[M]^{+\cdot}$, 341 (2) $[M-CO]^+$, 338 (11) $[M-OCH_3]^+$, 326 (33), 325 (>100) $[M-CO_2]^{+\cdot}$, 312 (11), 304 (48), 297 (11), 265 (15), 264 (100) $[M-COC_6H_5]^+$, 234 (30), 232 (15), 214 (26), 115 (80), 106 (>100), 105 (>100)	1742 (CO, $COOCH_3$), 1680 (COC_6H_5), 1635 (C=CH)

TABLE 4. Physical Parameters for IX-XVI

Compound	$[\alpha]_D^{20}$ (c = 1, $CHCl_3$)	Mobility		Yield, %	
		R_f (system)*	K (system)*	23 °C	60 °C
IX	+ 353	0,33 (B)	5,0 (B)	84	67
IXa	+ 131	0,42 (C)	8,5 (B)	—	21
X	+ 302	0,39 (B)	6,2 (B)	47	77
Xa	+ 119 (c = 0,62)	0,48 (C)	9,2 (B)	—	12
XI	+ 263	0,31 (B)	5,9 (B)	60	79
XII	+ 270	0,34 (B)	5,3 (B)	49	76
XIII	+ 253	0,45 (B)	2,0 (B)	60	73
XIV	+ 132	0,54 (B)	1,9 (B)	58	61
XIVa		0,40 (B)	2,5 (B)	—	14
XV	+ 205 (c = 0,73)	0,38 (B)	2,8 (B)	46	46
XVa	+ 182 (c = 0,5)	0,27 (B)	3,3 (B)	20	36
(*E*, *Z*)-XVI		0,52 (B) 0646 (B)	1,7 (B) (*E*-) 1,8 (B) (*Z*-)		48**

*For solvent system, see Table 1.

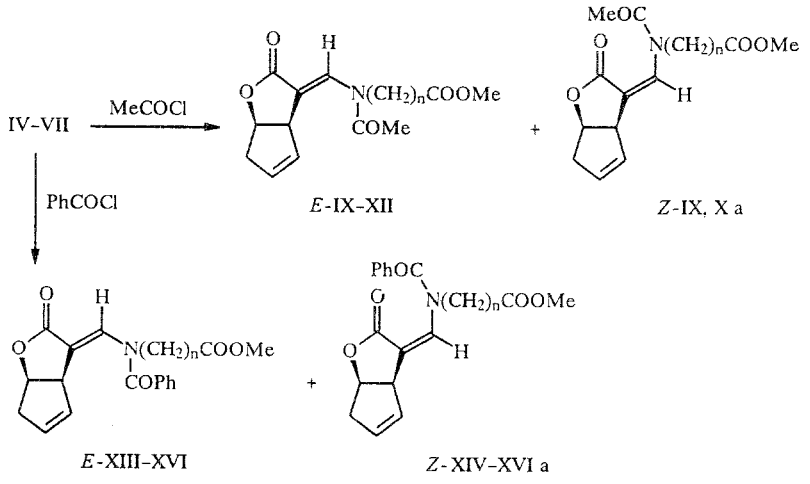
**In this case, 25% of unreacted starting material remained. The E- and Z-isomers could not be separated. Ratio of E/Z = 1/1 by PMR.

To investigate the acylation of IV-VII, we have studied their reaction with acetyl and benzoyl chlorides in the presence of dimethylaminopyridine in methylene chloride (Scheme 2). Acylation with acetic anhydride did not occur, even under reflux conditions (see Scheme 2, top of following page).

With acetyl chloride, the reaction is complete within 24-48 h and within 7-11 h when refluxed in dichloromethane. Acetylation of IV goes faster, evidently because of the greater mobility of the NH− proton. Only the E-form of the corresponding N-acetyl compounds IX-XII is produced from all the homologs at room temperature; the same happens when the homologs VI and VII are refluxed. However, acetylation of IV and V at increased temperature leads to formation of both the E- and Z-isomers, the latter actually in small yield (Table 4).

The PMR spectra of the E- and Z-forms of the acetylated compounds IX and X are most easily distinguished by the chemical shifts of the vinyl proton. Thus, in the Z-isomers there are high field shifts of this proton (0.43 ppm in IXa and 0.63 ppm in Xa) when compared with the corresponding E-forms.

The PMR spectra of IX show differences in the shifts of the $N-CH_2$ protons; in the Z-isomer they are equivalent and in the E-isomer they appear as two doublets (see Table 2).



The benzoylation of IV-VII at room temperature proceeds more slowly than the acetylation (76-96 h). When refluxed in dichloromethane, the reaction time for both reactions is approximately the same. An exception is VII (n = 4) which is not fully benzoylated under these conditions.

In contrast to acetylation, only in the case of the short homolog IV (n = 1, independently of the acylation temperature) and the homolog V (at room temperature) does benzoylation occur to give just the trans isomer of the corresponding N-benzoyl derivative. In all other experiments both the trans and cis products are formed and it is apparent that increasing the length of the homolog gives a trans/cis isomer ratio shifted somewhat to the trans form (see Table 4).

As a side product in the preparation of the N-benzoylamino derivative XIV at room temperature, we obtained the methyl ester of 3-(N-benzoyl)aminopropionic acid (33%). This is probably due to the lower stability of the homolog XIV when compared with the others.

Thus, for our β-aminovinyl lactones IV-VII acylation occurs exclusively on the nitrogen atom, as in the acylation of N-unsubstituted β-aminovinyl ketones [6]. Formation of two isomers of the N-acyl derivatives, in some cases, points to the occurrence of cis-trans isomerism for the compounds prepared. Raising the acylation temperature speeds up this process. A more bulky substituent on the nitrogen promotes the cis-isomer content of the corresponding N-benzoyl derivatives, as observed for β-aminovinyl ketones [6].

EXPERIMENTAL

PMR Spectra were obtained on Bruker WM-360 and WH-90 instruments using $CDCl_3$ solvent and TMS internal standard. Mass spectra were taken on a Kratos MS-50 instrument with ionization energy 70 eV. FAB Mass spectra were recorded on the same (Kratos WM-50) instrument fitted with an Ion Tech Ltd. FAB 11 NF source, argon ionization gas, and thioglycerol matrix. IR Spectra were taken on a Perkin–Elmer 580B spectrometer using $CHCl_3$ solvent. The optical rotations $[\alpha]_D^{20}$ were measured on a Rudolph Research (Flanders, New Jersey) Autopol II automatic polarimeter using $CHCl_3$ solvent.

Chromatography was performed using a Laboratorni pristroje Praha liquid chromatograph with a differential refractometer detector. Normal phase HPLC was performed using a 3.0 × 150 mm column filled with Separon TM SGX (5 μm) sorbent. Capacity factors were calculated using the equation $K = (t_r - t_0)/t_0$, where t_r is the retention of the sorbate and t_0 that of hexane. The solvent systems used are shown in Table 1. After extraction, the organic solutions were dried (Na_2SO_4) and evaporated in vacuo at a bath temperature not exceeding 40°C. The progress of the reaction was monitored using TLC on Silufol UV-254 plates. The spots were visualized by UV light and the plates were sprayed with a 10% solution of phosphomolybdic acid in ethanol and subsequently heated at 120°C. The target compounds were purified using column chromatography on Lachema Silasorb 600 silica gel.

(E)4-(Mesyloxymethylene)-2-oxabicyclo[3.3.0]-6-octene-3-one (II, $C_9H_{10}O_5S$). Methanesulfonyl chloride (0.2 ml, 2.6 mmole) in acetone (2 ml) was added dropwise with stirring at 0°C to a solution of the Na salt of α-formyl-γ-lactone (I, 0.4 g, 2.4 mmole) in water (2 ml). The temperature was increased to ambient and stirring continued for 30 min. The reaction mixture was treated with water and extracted with ethyl acetate. The crude material was purified by column chromatography on silasorb, eluting with system B and then C to give II (0.54 g, 98%).

(E+Z)4-Mesyloxymethylene-2-oxabicyclo[3.3.0]-6-octen-3-one (II + III, $C_9H_{10}O_5S$). Methanesulfonyl chloride (1 ml, 9.6 mmole) was added slowly with stirring at −15°C to a suspension of the Na salt of α-formyl-γ-lactone (I, 1.4 g, 8 mmole) in dry ether (8 ml) and held at this temperature for 1 h. Further treatment was as above to give II (1.2 g, 63%) and the cis-isomer III (0.6 g, 31%).

4-(Carbomethoxymethylaminomethylene)-2-oxabicyclo[3.3.0]-6-octen-3-one (IV, $C_{11}H_{13}NO_4$). A solution of the methyl ester of glycine hydrochloride (0.25 g, 2 mmole) and K_2CO_3 (0.3 g, 2.5 mmole) in methanol (3 ml) was stirred for 10 min. Compound II (0.23 g, 1 mmole) in methanol (2 ml) was added slowly and the mixture was held at room temperature for 21 h. It was dissolved in water and extracted with ethyl acetate. The crude material was chromatographed on silasorb and eluted using system D to give IV (0.14 g, 63%).

Compounds V-VII were obtained similarly (Table 1).

4-(Pyrrolidin-2-one-N-methylene)-2-oxabicyclo[3.3.0]-6-octen-3-one (VIII, $C_{12}H_{13}NO_3$). **A.** Stirring methyl γ-aminobutyrate hydrochloride (0.4 g, 2.5 mmole), K_2CO_3 (0.6 g, 4.2 mmole), and II (0.26 g, 1.1 mmole) in methanol (6 ml) for 40 h and column chromatographic purification of the crude product on silasorb using system E gave VIII (0.12 g, 56%). **B.** Al_2O_3 (Brockmann neutral grade II, 0.6 g) was added to a solution of VI (0.1 g, 0.4 mmole) in benzene (4 ml) and refluxed

for 5 h. Filtration, washing with benzene, evaporation, and column chromatographic purification of silasorb using system E gave VIII (0.07 g, 78%).

4-[Carbomethoxymethyl-N-(acetyl)aminomethylene]-2-oxabicyclo[3.3.0]-6-octen-3-one (IX, $C_{13}H_{15}NO_5$). Acetyl chloride (0.1 ml, 1.1 mmole) in dichloromethane (2 ml) was added to a solution of IV (0.08 g, 0.47 mmole) and dimethylaminopyridine (0.14 g, 1.1 mmole) in dichloromethane (4 ml). The mixture was stirred at room temperature for 24 h and then diluted with water and extracted with ethyl acetate. The crude sample was purified by column chromatography using silasorb and eluent system C to give IX (0.08 g, 84%).

Compounds X-XII were obtained similarly (see Table 4).

4-[Carbomethoxymethyl-N-(benzoyl)ami nomethylene]-2-oxabicyclo[3.3.0]-6-octen-3-one (XIII, $C_{18}H_{16}NO_5$). Benzoyl chloride (0.3 ml, 2.6 mmole) in dichloromethane (3 ml) was added to a solution of IV (0.23 g, 1.03 mmole) and dimethylaminopyridine (0.46 g, 3.8 mmole) in dichloromethane (4 ml). The product was refluxed for 13 h, cooled, diluted with water, and extracted with ethyl acetate. The crude sample was purified using column chromatography on silasorb using eluent system B to give XIII (0.24 g, 73%) with mp 107-109.5°C and R_f 0.45 (system B).

Compounds XIV-XVI were obtained similarly (see Table 4). The melting point of XV was 89.5-91°C.

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