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Attempted Diastereoselective Preparation and Chiroptical Properties of (2*S*)-1-(3-Mercapto-2-Methyl-1-Oxopropyl)-L-Proline (Captopril) and Some Congeners

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CD and ^{13}C-NMR study of the conformational properties of (2*S*)-1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (captopril, *1*), and its congeners *2*—*5*, *8*, *9* is reported. ^{13}C-NMR data (in DMSO-d_6) reveal an E/Z (*cis*/*trans*) ratio of ca. (15—30) : (70—85) for the N-acyl-prolines *1*, *5*, *10*, and for N-acetyl-L-proline. CD data indicate practically identical conformations for the ring systems of *8* and *9*. Attempted diastereoselective cyclization of the sodium salt of 7 or the free thioacid into *8* and *9* resulted in low chemical yields (~30%) and low diastereoselectivity, favouring formation of the »wrong« diastereomer *9* in small excess (~20%).

INTRODUCTION

Cushman, Ondetti et al.[1,2] recently discovered a new class of potent and highly specific inhibitors of the angiotensin converting enzyme (ACE), designed to complement the active structure of the hypothetic model of the ACE active site[3]. Clinical efficacy has been demonstrated for the orally active agent captopril (2*S*)-1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (*1*)[4,5], which has been successfully introduced into the therapy of hypertension[6–9].

Synthesis of captopril was first reported in an overall yield of 12%[1,2]. In the meantime, about 70 different patents on preparations of captopril were cited in Chem. Abstracts. Acylation of proline with various precursors of 3-mercapto-2-methyl-propionic acid was claimed in over 20 independent applications[7,10–17]. These methods require either a separation of diastereomers, e. g. *3* and *4*, without a possibility to recycle the »wrong« diastereomer, or the resolution of racemic 3-acetylthio-2-methyl-propionic acid by some chiral bases[18]. A chirally economic approach[19] to *1* would employ an enantioselective addition of thiocetic acid to methacrylic acid catalyzed by some chiral bases,

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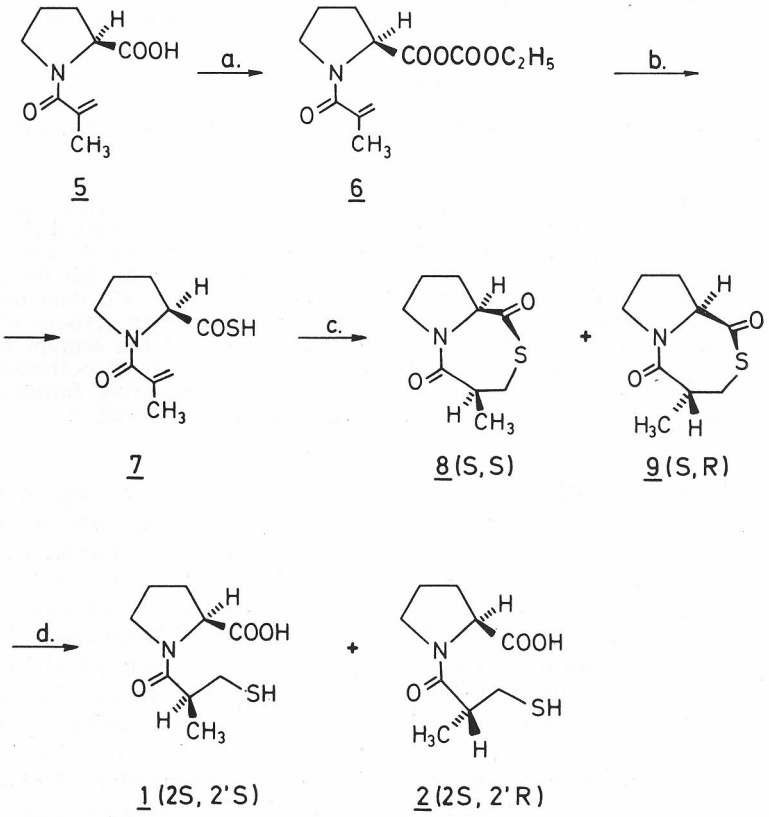
according to the method developed by Wynberg[20,21] who also indicated such a possibility in a review article[22].

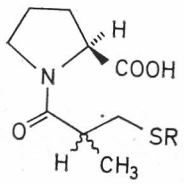
Cyclization of captopril (*1*) or its diastereomer *2* into thiazepine derivatives *8* and *9* has been claimed[23–26]. Most of these patents claim the hydrolytic opening of the 7-membered ring of *8* into *1*; some other patents claim a reductive cleavage of disulfide *10* into two moles of *1*[27–29].

The aim of our synthetic work was to circumvent separation of diastereomers *3* and *4*, which result from acylation of L-proline with racemic 3-acetylthio-2-methylpropionic acid[1,10–17], and to prepare *8* by diastereoselective cyclization, i. e. by intramolecular addition of the thiocarboxylic function in *7* (Scheme 1). Subsequent hydrolysis would then afford the desired product *1*.

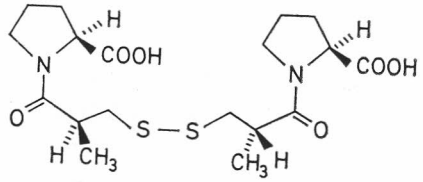
Scheme 1



a. Et_3N/ClCOOEt / THF, b. NaHS (dry) / THF, c. AcOH or CF_3COOH
d. 3N NH_3 / MeOH / 0 °C



	R	2, 2'	
1	H	(S, S)	(captopril)
2	H	(S, R)	
3	$COCH_3$	(S, S)	
4	$COCH_3$	(S, R)	



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To this end we performed a detailed study of the conformation of various open-chain and cyclic congeners of captopril (1), using CD and ^{13}C-NMR spectroscopy.

RESULTS AND DISCUSSION

^{13}C-NMR and CD Spectra and Conformational Analysis

In view of our concept of performing diastereoselective cyclization of *N*-methacryloyl L-thioloproline (*7*), an inherently unstable compound, we became interested in determining exactly the conformational properties of its congeners.

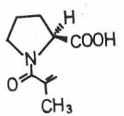
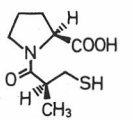
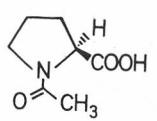
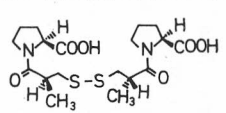
^{13}C-NMR spectroscopy has been repeatedly used to provide information regarding the conformation of *N*-acyl-prolines within and around the proline unit[30,31]. It was observed for simple acyl prolines that the shifts of C(2) and C(5) atoms, next to the proline nitrogen atom, are the most sensitive to shielding by the amide oxygen atom, and thus can be used to identify the presence of both conformers[32]. Recently, a group of Squibb authors[2] attempted to correlate the ACE inhibitory potencies with relative *E*/*Z* (*cis*/*trans*) populations of some *N*-acyl-L-prolines in aqueous solution as determined by ^{13}C-NMR spectroscopy. The Squibb group reported a ~50 : 50 ratio of *E*/*Z* (*cis*/*trans*) conformers of captopril (*1*) and some relater *tert.* amide derivatives. The concentration of the *E*-isomer (~50%) is surprisingly bigh in view of the fact that for TRH-hormone (H-L-Tyr-L-Hys-L-Pro-NH_2) it is ~20%[33].

We have measured the ^{13}C-NMR spectra quantitatively for *N*-acetyl-L--proline and for compounds *1*, *5* and *10* (Table I).

It was interesting to note that the conformational equilibrium for methacryloyl L-proline (*5*), as well as captopril (*1*), and its dimer (*10*), does not deviate significantly from *E*/*Z* (15—30) : (70—85), although determined in non--aqueous solution. Besides, the general ^{13}C- shift pattern for both derivatives

TABLE I

^{13}C-NMR Chemical Shifts and Relative Peak Hights of Selected N-acyl-L-Proline Derivatives[a,b]

Compd.	Structure		C(1)	C(2)	C(3)	C(4)	C(5)	C(1')	C(2')	C(3')	C(4')	Average peak ratio (*E*/*Z*)[d]
		δE	174.32	59.13	31.88	22.40	46.39	169.36	22.97			26.5:73.5
		%	33	25	24	25	25	25	25			
		δE	174.04	58.74	29.63	24.88	47.85	169.08	22.40			
		%	67	75	76	75	75	75	75			
5		δE	184.20	70.54	41.19	32.56	56.15	180.37	151.86	125.40	29.57	30.4:69.6
		%	28	31	30	75	75	29	32	31		
		δZ	183.46	68.57	39.16	34.93	59.03	179.46	151.46	126.53	29.57	
		%	72	69	70	72	69	71	68	69		
1		δE	174.27	59.43	28.38	22.74	45.56	173.08	—[c]	28.39	16.87	17.3:82.7
		%	18	17	—	17	17	18		—	—	
		δZ	173.98	59.03	28.38	24.89	47.18	173.76	—[c]	—	—	
		%	82	83	—	83	83	83		83	83	
10		δE	174.09	59.14	29.12	23.19	46.19	173.20	—[c]	—[c]	16.42	16.8:83.2
		%	16	16	—	15	15	16			25	
		δZ	173.70	58.80	29.12	24.89	47.12	172.69	—[c]	—[c]	16.93	
		%	84	84	—	85	85	84			75	

[a] Values in ppm related to TMS. [b] Determined in DMSO-d_6. [c] Peaks overlapped by DMSO-d_6 signlas. [d] *E*/*Z* ratio corresponds to *cis*/*trans* ratio, according to the previous notation for assigning conformation of N-acyl-L-prolines[13,32].

1 and *5* substituted in the side chain, and the dimer *10*, was the same as for the model compound N-acetyl-L-proline.

Additional information about the conformation of these N-acyl-L-prolines was obtained from the CD-spectra. For the model compound N-acetyl-L--proline two quite different CD spectra have been reported in the literature. In methanol solution Nishihara et al.[34] found $\Delta\varepsilon \sim 0.1$, at 238 nm, whereas we had reported —3.71 at 225 nm in acetonitrile[35]. We have, therefore, remeasured the solvent dependence of the CD and could in principle confirm both results: in ethanol, a very small Cotton effect at 239 nm ($\Delta\varepsilon - 0.15$) is recorded, and just below 200 nm another, much stronger one ($\Delta\varepsilon - 5$) appears. In acetonitrile, however, for the first band we have found again a pronounced negative effect ($\Delta\varepsilon - 5.92$) at 227 nm, and another one around 185 nm ($\Delta\varepsilon - 4$). Nishihara et al.[34] had for some related compounds ascribed such a striking variation of CD values with measuring conditions to the presence of different *E*/*Z* ratios. Althought this might be the main reason other conformational differencies might as well be responsible for these drastic changes of the CD. Even a coupling through the σ-bond skeleton may be involved in an appropriate conformation. The N-methacryloyl derivative *5* exhibits a strong negative CD in both solvents, in ethanol at 221 nm ($\Delta\varepsilon - 3$), and in acetonitrile at 230 nm ($\Delta\varepsilon - 4.3$), Figure 1.

This result reveals a much lower solvent dependence of conformational equilibria in *5* than in N-acetyl-L-proline, and one can assume that the preferred conformer in both solvents remains *Z*, as noticed by ^{13}C-NMR for DMSO solution.

Captopril *1* and its diastereomer *2* each contain the same two chromophores as the model compound N-acetyl-L-proline, namely the amide and carboxylic group. While the SH-group does not absorb above 190 nm, the

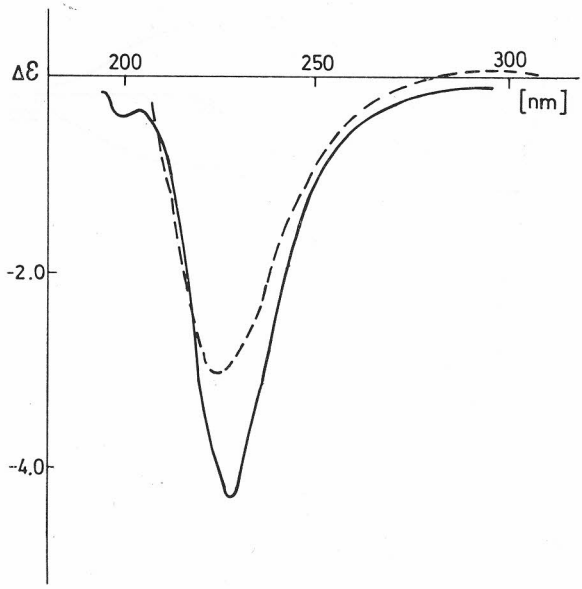


Figure 1. CD-spectra of *5* in acetonitrile (————) and ethanol (— — —).

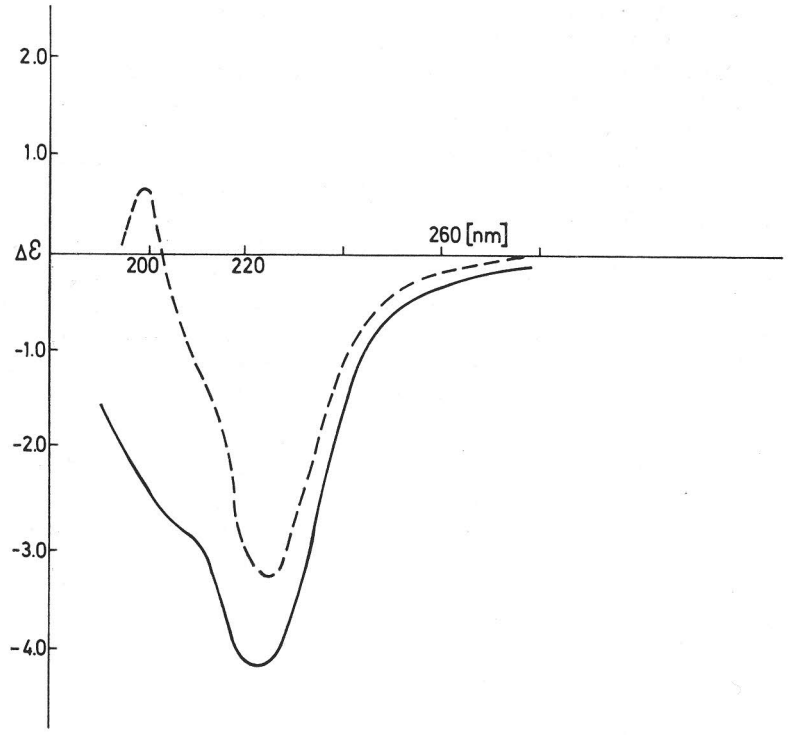


Figure 2. CD-spectra of *1* (————) and *2* (— — —) in acetonitrile

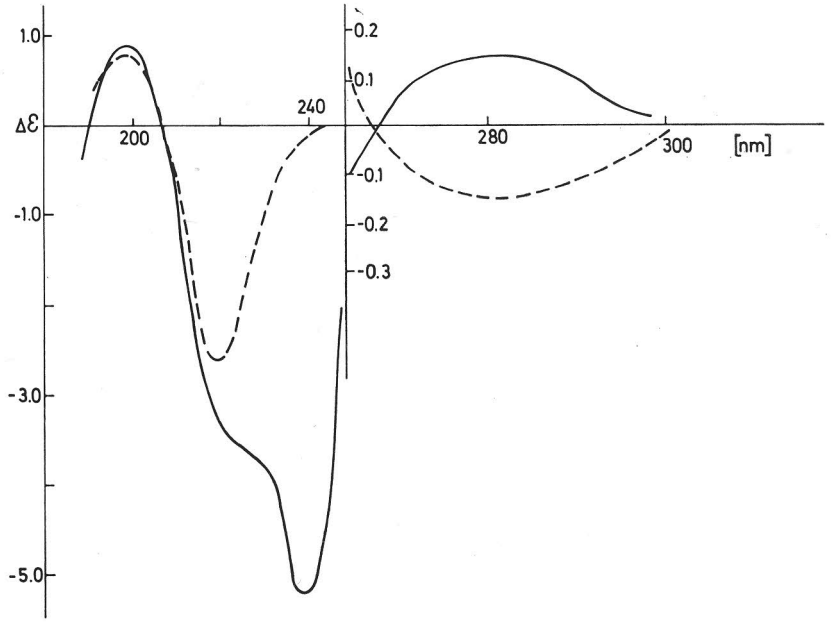


Figure 3. CD-spectra of *3* (————) and *4* (— — —) in acetonitrile.

S-acetyl group is reported to give rise to at least three Cotton effects around 270—310, 240 and 200 nm[36]. For *3* and *4* we expect, therefore, three corresponding CD-bands, and in addition two (around 220 and below 200 nm) from both the amide and the carboxylic acid chromophore. Since these two diastereomers differ only in the configuration of the side chain, we expect opposite signs for the Cotton effects of the S-acetyl chromophore, but the same ones for those of the other two chromophores.

The first Cotton effects around 280 nm are of opposite sign for *3* and *4*, and the same holds for those around 240—245 nm, which for *4* is rather small, but is the largest one in the CD spectrum of *3*. This great difference in magnitudes is a mere result of band overlap, since around 220 nm also the rather strong (negative) Cotton effect of the N-acyl chromophore is present, which must, of course, have the same sign for both diastereomers,

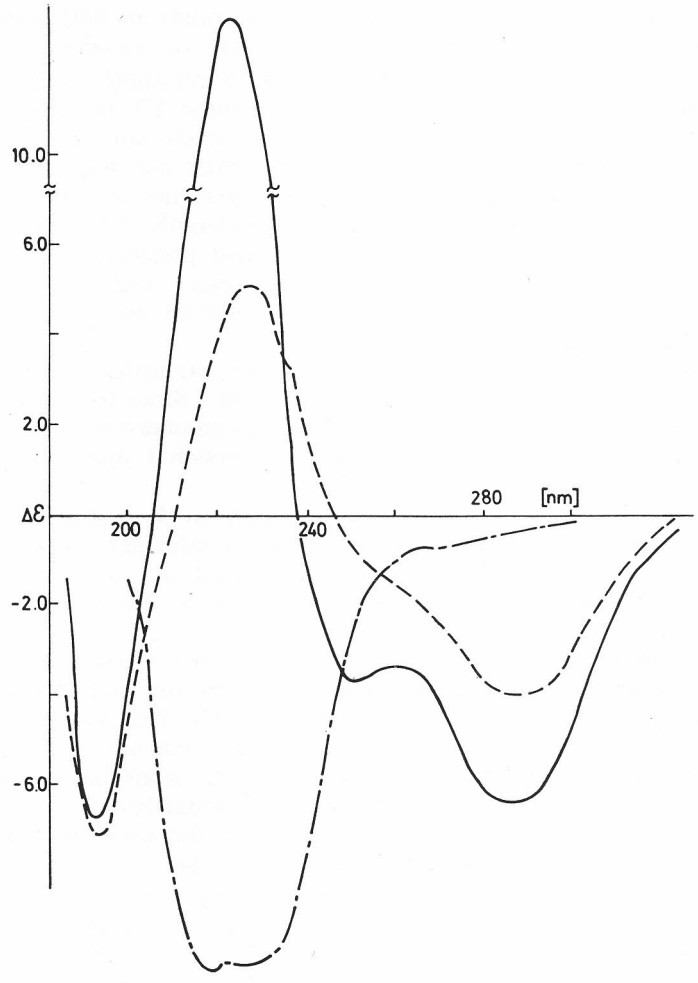


Figure 4. CD-spectra of *8* (————), *9* (— — —), and *10* (— · — · —) in acetonitrile.

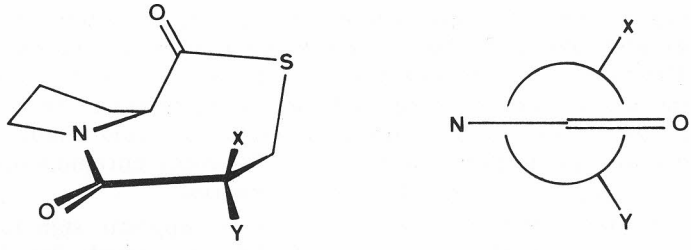


Figure 5. Approximate conformation of 8 and 9 (X, Y) = (H · Me). Left: Overall projection. Right: Newman-projection from C (=O) towards C (X, Y).

as has also the proper model compound N-acetyl-L-proline[34,35]. These first--mentioned CD bands must, therefore, be associated with the —S—Ac moiety, which is diastereomerically arranged in these two molecules. Another Cotton effect around 200 nm, positive and of same magnitude in both spectra, must then also be associated with the amide and/or acid chromophore.

Although the first Cotton effect of the S—S-chromophore is only weak it is nevertheless distinctly observable for *10* around 270 nm (Figure 4). The Cotton effect around 225 nm which is so characteristic of the N-acetyl L-proline moiety is further enhanced for *10*, which can either be due to a drastic change of the *E*/*Z* equilibrium, or to the presence of a negative Cotton effect of the S—S chromophore at the same wavelength. ^{13}C-NMR data (Table I) seem, however, to rule out the first mentioned possibility. We have then to conclude that also for the even slightly stronger negative Cotton effect at 210 nm this same (second) argumentation holds for parentage and size of this CD band.

The position of the first Cotton effect (270 nm) indicates that the torsional angle (C—)S—S(—C) is approximately +90°or —90°. Since for such a torsional angle the first two Cotton effects of the S—S-chromophore become degenerate, it does not seem possible to determine this torsional angle from the CD unequivocally[37].

The possibility that the thiocarboxy anion in *7* might preferentially approach the side chain of either the *Z* or the *E* conformer cannot be addressed by a spectroscopic study. Therefore, we analyzed in more detail the conformational properties of diastereomers *8* and *9*. Their CD spectra are given in Figure 4.

The CD spectra of the two diastereomers *8* and *9* show both four CD bands of identical sign pattern: negative around 280 nm and 250 nm, positive near 230 nm, and negative again below 200 nm. The first two Cotton effects are typical of the thiolactam chromophore, the third one is in analogy to the other cases assigned to the N-acyl prolyl moiety, while both chromophores could contribute to the last one. Surprising similarity of the CD-spectra points to the conclusion that the conformation of the seven-membered heteroring is similar for *8* and *9*, even in absolute sense.

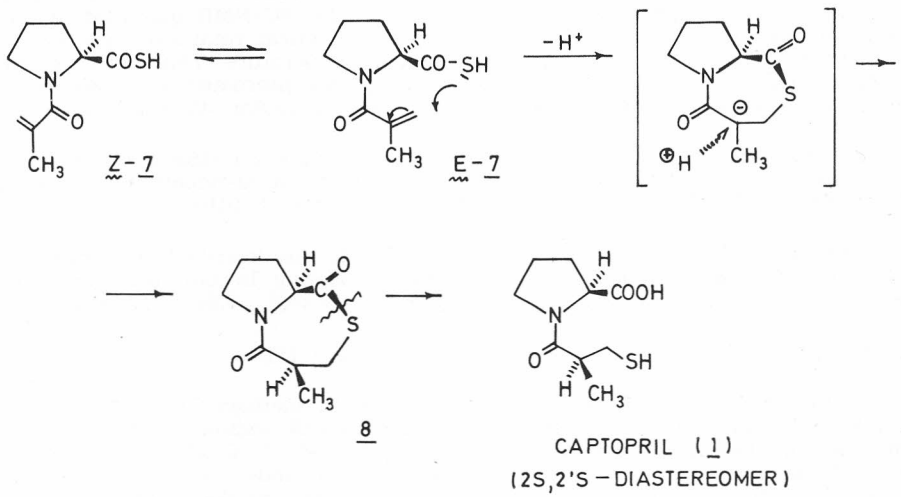
Although, in general, a seven-membered ring can adopt several conformations, this becomes impossible if two consecutive planar units of four atoms each are built into it. As models show, such a ring must always be strained, and taking into consideration the CD results, the conformation depicted in Figure 5 seems very probable. In this two (approximately) planar

units are merged together, which leads to a skew (*8*) or antiperiplanar (*9*) arrangement of the Me—C—C—S unit, with the C(=O) of the amide bisecting the H—C(—6)—Me moiety. If for the first $n \rightarrow \pi^*$ Cotton effect of a thiololactone the same rule holds as for the corresponding lactones, then the N-acyl nitrogen is expected to lead for *8* and *9* to similar negative Cotton effects. With nearly identical conformations of the seven-membered heterorings all other Cotton effects should then also be alike, which fits very well the two CD spectra.

Synthesis

We have envisaged a stereoselective approach to *1* which consists of an intramolecular stereoselective addition of the thiocarboxylic group in *E*-*7*, expecting *8* as the main product. The crucial intermediate *7* was prepared *via* *5*, according to the procedure of Jew et al.[39] and purified as dibenzylammonium salt *11*. An attempt to transform *5* into thioacid *7* by the methods

Scheme 2.



of Sheehan[40] and Cronyn[41] was unsuccessful. However, when freshly prepared anhydrous sodium hydrogen sulphide[42] was used, suspended in THF or acetonitrile, the sodium salt of *7* was formed quantitatively. This salt was unstable in organic solvents even when kept in refrigerator. The free acid, a highly viscous syrup, tends to polymerize, as well. During the attempted isolation it lost hydrogen sulphide, which is the generally known behaviour of thioacids at elevated temperature[43,44].

Consequently, we tried cyclizations of *7* *in situ*, exploring low temperatures and different solvent systems. Surprisingly, cyclization turned out to be a sluggish and unfavourable reaction, although intermolecular addition of thioacids to a double bond represents an easy reaction[2,7]. Diastereomeric

mixture *8/9* was isolated after chromatography on silica gel in ~ 30% yield. The diastereomeric excess did not exceed 20%, however, and the »wrong« diastereomer *9* regularly prevailed — see Experimental. This result, though disappointing from the conceptual point of view, can tentatively be explained by the similar population and reactivity of both conformers in *7* to those determined for *5*. Thus, neither the conformation in *7* nor the relative stabilities of products *8* and *9* favour formation of one of them, both being formed in approximately equal yield.

It is interesting to note that no six-membered thiolactone was isolated on cyclization of *7*, although the oxygen-analogue *5* afforded on bromolactonization only the six-membered lactone[39]. Finally, compounds *8* and *9* were converted with high yields into *1* and *2*, respectively, using the procedure described previously[16,45].

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage (Boetius) and have not been corrected. IR spectra (KBr pellets) were obtained with a Perkin Elmer M 297 spectrophotometer (only strong bands are indicated). NMR spectra were run on a Perkin Elmer R 12 instrument with TMS as an internal standard; shifts are given in ppm values downfield from TMS. ^{13}C-NMR quantitative spectra were obtained on a Varian FX90 Q instrument. Optical rotations were measured on a Perkin Elmer 141 polarimeter at ambient temperature. Thin layer chromatography (TLC) was performed on aluminium plates precoated with Merck silica gel 60 F_{254}. Column chromatography was run over granular silica gel 0.05—0.2 mm (Merck).

CD Spectra were obtained on a Dichrograph Mark III (ISA-Jobin-Yvon) connected on line to PDP-8e. Noise was eliminated by curve-smoothing according to Golay-Savitzky[46] algorithm (best parabola of degree 3 fitted to 25 consecutive points[7]).

Compounds *3* and *4* were prepared according to the described procedures[7] while compound *10* was obtained from *1*, on brief standing in buffered (pH 7.2) and aerated aqueous solution, mp 224—226°, $[\alpha]_D$ = —198.8 (c = 3.05 in EtOH).

N-Methacryloyl-S-proline-dibenzylammonium salt (11)

L-Proline (20.8 g, 0.18 mol) was acylated with methacryloyl chloride (28.2 g, 0.27 mol) in the solvent mixture acetone (200 ml)-2N sodium hydroxide (220 ml) maintaining the inner temperature at —10° to —5 °C. Crude product (18.3 g), isolated on partial evaporation, adjusting pH to 1 under ice cooling, extraction (ether, 3 × 100 ml) and evaporation of dried extracts was dissolved in hot ethylacetate (18.3 in 60 ml), and a solution of dibenzylamine (21.7 g, 0.11 mol) in ethylacetate, preheated to 50 °C, was added at once. After brief stirring, crystallization began, stirring was continued for 1 hour at ambient temperature, then the solution was deposited on ice for 6 hours. Pure *11* was collected on filter, washed with ethylacetate and dried affording 36.5 g (96%, based on the crude *5*), mp 128—130 °C, IR: 2400—3000, 1650, 1609, 1565, 1495, 1450, 1395, 747, 698 cm^{-1}. Anal. for $C_{23}H_{28}N_2O_3$ (380.49) Calc'd: C 72.58; H 7.42; N 7.36%. Found: C 72.80; H 7.30; N 6.39%.

N-Methacryloyl-S-thioloproline (7)

Compound *5* (18.3 g, 1.10 mol) obtained from dibenzylammonium salt by dissolution in water, adjustment of pH to 1—1.5, extraction with ether (4 × 80 ml), drying and evaporation of the solvent, was dissolved in dry THF (170 ml). Triethylamine (10.1 g, 0.1 mol) was added dropwise under stirring and cooling to 0 °C, and then a solution of ethylchloroformate (10.8 g, 0.1 mol) in dry THF (20 ml). After 2 hrs of stirring below 10 °C, the precipitated triethylamine hydrochloride was filtered off (13.2 g, 96%) and washed with THF (5 × 10 ml). The filtrate with crude

6 was added during 15 min., under vigorous stirring, to a suspension of dry sodium hydrogensulphide (5.7 g, 0.11 mol) in dry THF (100 ml) maintaining the temperature below 10 °C.

During this addition, reversible decoloration of the deep-yellow suspension was noticed; this effect persisted for 0.5—1 min. The reaction mixture was stirred at ambient temperature for additional 2 hrs. during which period the formation on only one iodoplatinate positive spot at Rf ~ 0.35—0.4 (ethylacetate-ethanol 6.5 : 3.5) was noticed. A 20 ml aliquot was evaporated to dryness at ambient temperature, the residual oil was dissolved in ice-water (50 ml), pH adjusted to 4, and the cold aqueous solution extracted with methylenechloride (3 × 30 ml). Combined organic extracts were dried (Na_2SO_4, in refrigerator), evaporated at ambient temperature and the residual oil (7) was dried at 0.1 mm Hg/P_2O_5. IR ($CHCl_3$): 2850—3000, 1685, 1650, 1620, 1450, 1420, 1325, 1015, 872 cm^{-1}.

All attempts to obtain a pure sample of 7, either by chromatography on silica gel or by crystallization, failed because of its progressive decomposition. When THF solution of the sodium salt of 7 was kept cold for some days, two spots of *8* and *9* appeared on the TLC plate, together with those of many other decomposition products.

(4S,9aS) and (4R,9aS)-Hexahydro-4-methyl-[1H,5H]-pyrrolo[2,1-c]-[1,4]thiazepine-1,5-diones, (8 and 9) — General procedure

Sodium salt of 7 (ca. 2.0 g, 10 mmol obtained on evaporation at room temperature of 50 ml of THF solution from previous preparation) was dissolved in acetonitrile (80 ml). To the resulting solution, borotrifluorid etherate (12 mol) was added dropwise at —15 °C. The reaction mixture was stirred under nitrogen for 12 hrs. Thereafter the solvent was evaporated to dryness, the product mixture dispersed in ice-cold bicarbonate solution (20 ml), extracted with ethylacetate (3 × 30 ml), the organic extracts were dried (Na_2SO_4), evaporated and the crude product was deposited on a silica gel column (80 g). Slow eluation with ethylacetate-ethanol (9.0 : 1.0) afforded a pure mixture *8/9* (540 mg, 27%). This mixture was rechromatographed on 25 g silica gel column, using ethylacetate-chloroform--methanol (8.5 : 1.0—0.5) as eluent. In fractions 9—14 (5 ml per fraction) 190 mg (9.5%) of pure *8* were obtained, the fractions 15—17 contained ca. 1 : 1 *8/9* mixture (140 mg), while fractions 18—23 contained 260 mg (13.2%) of pure *9*. Compound *8* was further purified by crystallization from ethylacetate-ether, mp 98—101 °C, $[\alpha]_D$ — 114.9 (c = 0.80 in EtOH) (lit.[39] mp. 103—104 °C, $[\alpha]_D$ — 113.6 (c = 0.835 in EtOH).

Compound *9* was repeatedly purified on a 10 g silica gel column, using ethylacetate-chloroform (8.0 : 2.0) as eluent, and by crystallization from ethylacetate-light petroleum, mp. 80—82 °C, $[\alpha]_D$ = —42.0 (c = 0.66 in EtOH) (lit.[39] mp. 74—76 °C, $[\alpha]_D$ = —36.02 (c = 0.66 in EtOH)).

According to this method of cyclization and isolation of *8* and *9*, the following results were obtained with other solvents and conditions:

a) Sodium salt of 7 dissolved in CF_3COOH at —5° to — 10°, then stirred for 48 hrs — total yield 21.6%, *8/9* ratio 42 : 58.

b) Sodium salt of 7, 2.5 mol in THF solution as prepared in the previous example was cooled to 0 °C, borotrifluorid etherate (4.0 mol was added and the reaction mixture stirred at ambient temperature for 24 hrs. Total yield *8/9* was 24.2% the ratio was 47 : 53.

c) The isolated sodium salt of 7 (10 mmol) was immediately dissolved in DMSO (20 ml) and cooled to 0 °C. After stirring for 24 hrs., the solvent mixture was evaporated at 1—2 mmHg and the crude syrup was purified on silica gel column to afford 750 mg (23.5%) of mixture *8/9*, which contained 61% of *9* (22% diastereomeric excess).

(2S)-1-(3-Mercapto-2-methyl-oxopropyl)-L-proline (1)

Thiolactone *8* (0.26 g, 1.3 mol) was dissolved under ice cooling in 5 ml of 3N methanolic ammonia. This mixture was stirred under nitrogen for 1 hr at 0 °C and 1 hr at ambient temperature. The solvent was removed *in vacuo* and the residue was purified on a short column of Dowex 50W × 4 by eluating with water.

Crude *1* (0.26 g, 92%) was crystallized from ethylacetate-cyclohexane affording 0.14 g of pure *1*, mp. 103—106 °C, $[\alpha]_D$ — 131.1 (c = 3.55 in EtOH) (lit.[1] mp. 87—88°, resolidification and melting at 104—105 °C, $[\alpha]_D$ — 131.0 (c = 1.7 in EtOH).

(2R)-1-(3-Mercapto-2-methyl-oxopropyl)-L-proline (2)

Starting from thiolactone *9*, compound *2* was obtained in the same manner as described for *1*, mp. 98—99 °C, $[\alpha]_D$ — 41.2 (c = 2.3 in EtOH).

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SAŽETAK

Pokušaj dijastereoselektivne priprave i kiroptička svojstva S-1-(3-merkapto)-2-metil-1-oksopropil-L-prolina (captopril) i nekih srodnika

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Izvještava se o CD-^{13}C-NMR studiju konformacijskih svojstava S-1-(3-merkopto)-2-metil-1-oksopropil-L-prolina (captopril, *1*) i njegovih srodnika *2*—*5*, *8*, *9*. Podaci ^{13}C-NMR (u DMSO-d_6) pokazuju omjer *E*/*Z* (*cis*/*trans*) za N-acil-proline *1*, *5*, *10*, te N-acetil-L-prolin, koji varira između 15—30 : 70—85. CD podaci ukazuju da ciklički produkti *8* i *9* posjeduju slične konformacijske osobine, tj. konformaciju poput stolice sa praktično jednakom geometrijom oko jedinice C—S—C(=O)—C—N—(=O). Pokušaj diastereoselektivne ciklizacije natrijeve soli tiokiseline (*7*) ili slobodne kiseline, u spoj *8* i *9*, rezultirao je niskim kemijskim iskorištenjem (~ 30%) i niskom diastereoselektivnošću, favorizirajući »krivi« diastereomer *9* u malom višku (~ 20%).