SYNTHESIS AND ABSOLUTE CONFIGURATION OF 1,7-DIAZASPIRO[4,4]NONANE-2,6-DIONE*

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Synthesis and determination of absolute configuration of the title compound are described and its CD spectrum is presented.

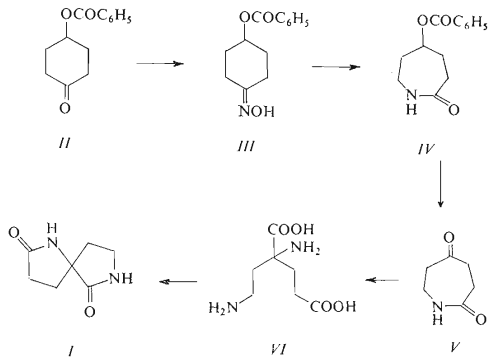
The most important factor, influencing the optical activity of peptides, appears to be the system of homoconjugated amide (peptide) groups. In this context, three structural features can be considered: (*i*) positional isomerism of amide groups in the molecule, (*ii*) conformational relation between amide groups, and (*iii*) conformation of amide groups as such (*cis-trans* isomerism, planarity or non-planarity). Conformational aspects of chiroptical properties of two homoconjugated *cis*-amide groups and chiroptical properties of non-planar amide groups have been studied on a series of model compounds by the Prague group[1-3]. In the preceding paper Kajtár and coworkers[4] described the synthesis of three constitutionally isomeric spiro-dilactams as models for investigating the correlation between chiroptical properties and relative position of two *cis*-amide chromophores, fixed in a molecular framework. In this communication we report the synthesis and determination of absolute configuration of a further member of this family, 1,7-diazaspiro[4,4]nonane-2,6-dione (*I*).

Synthesis

Two approaches, developed independently in our Laboratories, were chosen. The first (Scheme 1) consisted in preparation of the racemic dilactam *I* which was then subjected to optical resolution by chromatography on an optically active adsorbent (for analogy see ref.[3]). This synthesis started from 4-benzoyloxycyclohexanone[5] (*II*) which was converted into its oxime *III* and subjected to Beckmann rearrangement. The product *IV* was saponified and oxidized to give the keto lactam *V* which on Strecker synthesis afforded the diamino diacid *VI*. This was cyclized to the desired spiro-

* Part II in the series Spiro-bis(2-pyrrolidinones); Part I: This Journal *47*, 936 (1982).

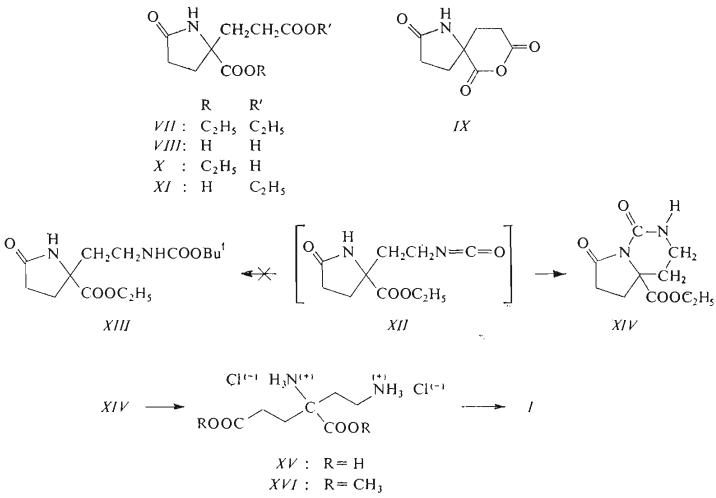
dilactam *I* by heating. The racemic product was only partially resolved by repeated column chromatography on triacetylcellulose and was obtained in an optical purity of about 30%.



SCHEME 1

The second approach used an optically active precursor from the very beginning and led to optically pure material, similarly as described in the preceding paper[4]. The starting compound was ethyl 2-ethoxycarbonyl-5-oxo-2-pyrrolidinepropanoate[6] (*VII*) (Scheme 2). Alkaline hydrolysis of *VII* led to the dicarboxylic acid *VIII* which was resolved into enantiomers with quinine. The subsequent steps of the synthesis were carried out starting from both the racemate and the two enantiomers of *VIII*. By treatment with hot acetic anhydride, the dicarboxylic acid *VIII* was converted into the cyclic anhydride *IX*. The alcoholysis of the latter led to a mixture of two monoethyl esters which were separated by crystallization and column chromatography. The isomeric structures *X* and *XI* were assigned to the two isolated substances on the basis of their mass spectra. One of the products (m.p. 123°C) exhibits the most abundant peak in the mass spectrum at *m/e* 156 (M−73), the corresponding fragment ions originating from the loss of either the $COOC_2H_5$ or the CH_2CH_2COOH side chain. The base peak in the mass spectrum of the other substance (m.p. 114°C) at *m/e* 184 (M - 45) is due to the loss of a COOH group, while another peak of smaller intensity (16%) at *m/e* 128·0340 ($C_5H_6NO_3$) can be assigned to the fragment ion formed by elimination of the $CH_2CH_2COOC_2H_5$ side chain.* On the basis of these

* The main process in the fragmentation of these compounds on electron impact is the fission of the bond between the pyrrolidinone ring and one of the side chains, with the positive charge remaining on the ring carbon atom where it is stabilized by the neighbouring nitrogen atom[7].



SCHEME 2

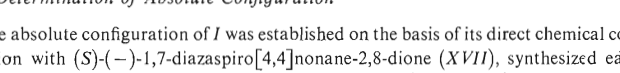
observations the assignment of structure *X* to the former substance and structure *XI* to the latter is justified. Also the pK_a values 4·53 and 3·42 found for the mono esters *X* and *XI*, respectively, are in agreement with the above assignment. In the alcoholysis of the anhydride *IX*, the two monoethyl esters *X* and *XI* were formed in a ratio of about 2 : 1, as determined by thin layer chromatography. This shows that the product distribution is controlled by the difference in the electrophilicity of the carbonyl groups of *IX* rather than by steric effects.

As the next step for a reasonable synthesis of the dilactam *I* (ref.[4]), we wanted to perform the replacement of the carboxyl group of *X* by an amino group by the modified Curtius degradation described by Shioiri and coworkers[8]. Compound *X* was heated with diphenyl phosphoroazidate and triethylamine in tert-butyl alcohol. The analytical and ^{1}H NMR spectroscopic data of the isolated crystalline product showed, however, that the isocyanate intermediate *XII* did not react with tert-butyl alcohol to give the expected urethane *XIII*, but was transformed, by an intramolecular addition, into the bicyclic compound *XIV* (Scheme 2). The latter was prepared in a better yield (66%) when, instead of tert-butyl alcohol, dichloromethane and toluene were used as solvents. The optical purity of (+)-*XIV* obtained from (+)-*X* was determined by the optishift technique[6] to be at least 96%.

Starting from *XIV*, the dilactam *I* was prepared in the following way (Scheme 2). Heating of *XIV* in 6M-HCl resulted in the hydrolytic fission of both rings and yielded the dihydrochloride *XV* of 2-amino-2-(2-aminoethyl)glutaric acid (*VI*). This salt, obtained in a chromatographically pure state, was converted without any further purification into the dimethyl ester hydrochloride *XVI* by treating with thionyl chloride in methanol. The dimethyl ester, liberated from the dihydrochloride *XVI* with triethylamine in methanol, transformed spontaneously into the dilactam *I*. The latter was obtained in 40% yield. By the above procedure the racemate as well as the two enantiomers of *I* were prepared. The constitution of the dilactam *I* is supported by its mass, IR, ^{1}H and ^{13}C NMR spectra. The crystal and molecular structure of *I* was determined by X-ray diffraction[9,10].

Determination of Absolute Configuration

The absolute configuration of *I* was established on the basis of its direct chemical correlation with (*S*)-(−)-1,7-diazaspiro[4,4]nonane-2,8-dione (*XVII*), synthesized earlier by Kajtár and coworkers[4]. By reduction with Red-Al (sodium bis(2-methoxyethoxy)-dihydridoaluminate) both *I* and *XVII* could be converted into 1,7-diazaspiro[4,4]-nonane (*XVIII*). Since the optical activity of this compound with no chromophoric group absorbing above 200 nm cannot be measured correctly when using small quantities, *XVIII* was transformed into its bis-N-nitroso derivative *XIX*, and the CD spectrum of the latter was recorded. The maxima found in the CD spectra of *XIX* obtained from (+)-*I* on the one hand, and from (*S*)-(−)-*XVII*, on the other, were of opposite signs, indicating that (+)-*I* has the (*R*) configuration. For sake of clarity, the formula of the (*R*)-(+)-enantiomer of *XVII* is shown in the Scheme 3.



(*R*)-(+)-*I* (*R*)-*XVIII*: Q = H; (*R*)-(−)-*XIX*: Q = N=O (*R*)-(+)-*XVII*

SCHEME 3

Knowing the absolute configuration of *I*, we can assign the configuration also to all the intermediates *VIII*, *IX*, *X*, *XI* and *XIV*.

The CD spectra of the optically active compounds synthesized by us are given in the Experimental. A detailed analysis of the chiroptical properties of the dilactam *I*, and the other isomeric spiro-bis(2-pyrrolidinones)[4] will be presented in another publication.

EXPERIMENTAL

All melting points are uncorrected and were measured on a Tottoli apparatus. The analytical samples were dried *in vacuo* over P_2O_5 for 8—10 h at appropriate temperatures. Thin layer and column chromatography were performed on silica-gel (Kieselgel F_{254} DC-Fertigplatten and Kieselgel 60, respectively) using the following solvent mixtures: (*a*) ethyl acetate–pyridine–acetic acid–water (30 : 11 : 3 : 6), (*b*) ethyl acetate–pyridine–acetic acid–water (43 : 4 : 1 : 2), (*c*) chloroform–ethanol (4 : 1), (*d*) benzene–ethanol (5 : 1) and (*e*) butanol–pyridine–acetic acid–water (30 : 20 : 6 : 24). Optical rotations were measured on a Zeiss Polamat polarimeter. IR, UV, ^1H and ^{13}C NMR, mass and CD spectra were recorded on Zeiss IR-75, Zeiss Specord, Varian XL-100, AEI MS 902 and Roussel-Jouan Dichrograph III (Jobin-Yvon) instruments, respectively.

4-Benzoyloxy-1-oximinocyclohexane (*III*)

A solution of 4-benzoyloxycyclohexanone[5] (*II*) (43·6 g) in methanol (220 ml) was mixed with a solution of hydroxylamine hydrochloride (15 g) and sodium acetate trihydrate (31 g) in water (100 ml) and the mixture set aside overnight. The precipitate was filtered, washed with water and dried, affording 31·9 g of the oxime. Further product (8·0 g) was obtained from the mother liquors; total yield 86% of the crude product which was used in the subsequent preparation. An analytical sample, m.p. 106—107°C, was obtained by crystallization from methanol. For $C_{13}H_{15}NO_3$ (233·3) calculated: 66·94% C, 6·48% H, 6·00% N; found: 66·48% C, 6·60% H, 6·23% N. IR spectrum ($CHCl_3$, cm^{-1}): 915, 1 665 sh, 3 270, 3 590 (C=N—OH), 1 712, 1 277 ($OCOC_6H_5$).

5-Benzoyloxy-2-azacycloheptanone (*IV*)

The crude oxime *III* (11·4 g) was rapidly introduced into virogously stirred polyphosphoric acid (100 g), preheated to 110°C, the temperature being kept at 105—108°C. After stirring at 108°C for 1 min the mixture was rapidly cooled, decomposed with a mixture of ice and chloroform and extracted four times with chloroform. The organic layer was washed with water and sodium hydrogen carbonate solution, dried over sodium sulfate and taken down. Crystallization of the residue from ethyl acetate afforded 9·5 g (83%) of the product, m.p. 133·5—135°C. For $C_{13}H_{15}NO_3$ (233·3) calculated: 66·94% C, 6·48% H, 6·00% N; found: 66·75% C, 6·48% H, 6·13% N. IR spectrum ($CHCl_3$, cm^{-1}): 1 669, 3 230, 3 305, 3 420 (CONH), 1 713, 1 277 ($OCOC_6H_5$); ^1H NMR spectrum ($CDCl_3$): 2·08 m, 4 H (2 × CH_2), 2·20—3·0 m, 2 H (CH_2—C=O), 3·0 to 3·7 m, 2 H (N—CH_2), 5·33 m, 1 H (OCO—CH), 7·15 broad, 1 H (NH), 7·20—7·70 m, 3 H (aromatic protons), 8·0—8·20 m, 2 H (aromatic protons).

2-Aza-1,5-cycloheptanedione (*V*)

A solution of the lactam *IV* (39·7 g) in methanol (250 ml) was mixed with aqueous sodium hydroxide (12·2 g in 180 ml water). After standing for 4 h at room temperature the mixture was neutralized with dilute hydrochloric acid, concentrated *in vacuo* to half of the original volume, acidified with hydrochloric acid and extracted three times with ether. The aqueous layer was neutralized (pH 7·0) with a solution of sodium hydrogen carbonate and concentrated (70 ml). The residue was dissolved in water (400 ml) and under stirring treated with sodium periodate (85 g) and $RuCl_3(OH)$ (50 mg) in acetone (900 ml). The mixture was set aside overnight, the inorganic material filtered off, washed with acetone and the filtrate taken to dryness. The residue was extracted four times with dichloromethane, the extract taken down and the residue crystallized from acetonitrile, m.p. 140—141°C, yield 11·3 g (52%). For $C_6H_9NO_2$ (127·1) calculated: 56·68% C, 7·13% H,

11·02% N; found: 56·70% C, 7·19% H, 10·99% N. IR spectrum ($CHCl_3$, cm^{-1}): 1 706 (C=O), 1 354, 1 675, 3 090, 3 225, 3 310, 3 415 (CONH). ^1H NMR spectrum ($CDCl_3$): 2·50–2·75 m, 6 H (3 × CH_2), 3·35–3·55 m, 2 H (N—CH_2), 7·51 broad, 1 H (NH).

4-Carboxy-4,6-diaminohexanoic Acid (*VI*)

A mixture of the ketolactam *V* (9·3 g), ammonium chloride (7·8 g), potassium cyanide (9·3 g), water (70 ml) and conc. aqueous ammonia (20 ml) was set aside at room temperature for 24 h. The mixture was then refluxed with conc. hydrochloric acid (250 ml) for 8 h, evaporated to a small volume, the precipitated salts filtered, washed with conc. hydrochloric acid and the filtrate taken to dryness *in vacuo*. The residue was dissolved in water and applied to a column of Dowex 50 (400 ml). After washing with water to neutral reaction of the eluate, the product was eluted with dilute (1 : 10) aqueous ammonia, the eluate taken down and the residue coevaporated twice with water, affording 10·6 g (76%) of the product *VI* which was used further without purification. An analytical sample, precipitated from an aqueous solution with acetone, decomposed in the range 222–227°C, depending on the heating rate. The product analyzed for the hemihydrate. For $C_7H_{14}N_2O_4.1/2\,H_2O$ (199·2) calculated: 42·20% C, 7·59% H, 14·06% N; found: 42·69% C, 7·60% H, 14·25% N.

(±)-2-Carboxy-5-oxo-2-pyrrolidinepropanoic Acid (*VIII*)

A solution of the diester[6] *VII* (51·5 g) in ethanol (500 ml) was added dropwise to a stirred 2M-NaOH solution (300 ml) in a period of 4 h at room temperature and set aside for 6 h. The solution was concentrated to about 200 ml and passed through a column filled with Varion KS cation exchange resin (H^+-cycle, 700 ml). The column was subsequently washed with water until the eluate became neutral (pH 6). The aqueous solution and the washings were concentrated to about 100 ml under reduced pressure. The crystals deposited after standing for several h in the refrigerator were collected and crystallized from water to yield 28 g (71%) of the racemic dicarboxylic acid *VIII*, m.p. 147–148°C; R_F (*a*): 0·27. For $C_6H_{11}NO_5$ (201·2) calculated: 47·76% C, 5·51% H, 6·96% N, 39·76% O; found: 47·73% C, 5·62% H, 6·78% N, 39·39% O; neutralization equivalent 100·7. IR spectrum (KBr, cm^{-1}): 3 600–2 350 (O—H), 3 245 (N—H), 1 735, 1 695, 1 630 (C=O).

Resolution of Acid *VIII* into Enantiomers ((*S*)-(+)-*VIII* and (*R*)-(−)-*VIII*)

A hot solution of the racemic dicarboxylic acid *VIII* (40·2 g) in ethanol (180 ml) was added to a hot ethanolic solution of anhydrous quinine (64·8 g in 350 ml). The crystals separated after standing for one day at room temperature were collected and crystallized five times from minimum amounts of ethanol. After each crystallization a sample (100 mg) of the quinine salt was transformed into the acid (see below) whose specific rotation and $\Delta\varepsilon$ value of the first maximum in the CD spectrum were determined. After the fifth crystallization no further increase in the optical activity of the acid could be detected. The optically pure quinine salt (20·6 g; m.p. 202–203°C) was dissolved in water (100 ml) and treated with Varion KS. The resin was filtered off, washed until neutral with water, and the aqueous solution, together with the washings, was evaporated under reduced pressure. The solid residue was crystallized from water to give 6·8 g (17%) of the optically pure (*S*)-(+)-*VIII*, m.p. 154–155°C; R_F (*a*) 0·27; $[\alpha]_D^{23}$ +18·3° (*c* 2; water). For $C_6H_{11}NO_5$ (201·2) calculated: 47·76% C, 5·51% H, 6·96% N; found: 47·60% C, 5·65% H, 6·85% N. IR spectrum (KBr, cm^{-1}): 3 600–2 335 (O—H), 3 230 (N—H), 1 725, 1 630 (C=O). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 210·5 (−4·41), 199·5 (0), 190 (+4·61).

The first mother liquor from the resolution procedure (about 500 ml) was evaporated and the remaining quinine salt (42 g) transformed into the acid by the method described above. The crude dicarboxylic acid obtained after evaporation of the aqueous solution (14 g) was crystallized two times from water to yield 5·1 g (12%) of the optically pure (*R*)-(−)-enantiomer of *VIII*, m.p. 154—155°C; R_F (*a*) 0.27; $[\alpha]_D^{23}$ −18·6° (*c* 2; water). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 210 (+4·48), 199 (0), 190 (−4·75).

(±)-2-Carboxy-5-oxo-2-pyrrolidinepropanoic Anhydride (*IX*)

Powdered racemic dicarboxylic acid *VIII* (20·1 g) was added in one portion to hot (100°C) acetic anhydride (200 ml), and the mixture was kept at 100°C for 10 min with occasional shaking. The clear solution was cooled to 40°C and evaporated at the same temperature under reduced pressure (130 Pa). This procedure was then repeated. The crude anhydride *IX* was obtained in quantitative yield (18·3 g) as a powder and was used in the next step without further purification. For analysis, a sample was crystallized from acetonitrile, m.p. 167—168°C. For $C_8H_9NO_4$ (183·2) calculated: 52·46% C, 4·95% H, 7·64% N, 34·94% O; found: 52·77% C, 5·06% H, 7·49% N, 34·90% O. IR spectrum (KBr, cm^{-1}): 3 235 (N—H), 1 800, 1 755, 1 700, 1 655 (C=O).

(*R*)-(+)-*IX* and (*S*)-(−)-*IX*

Both enantiomers of the dicarboxylic acid *VIII* were transformed by the above-described procedure into the corresponding optically active anhydrides *IX* in almost quantitative yield. The enantiomer (*R*)-(−)-*VIII* afforded (*R*)-(+)-*IX*, m.p. 185—187°C (from acetonitrile); $[\alpha]_D^{23}$ +41·1° (*c* 2, acetonitrile). For $C_8H_9NO_4$ (183·2) calculated: 52·46% C, 4·95% H, 7·64% N, 34·94% O; found: 52·30% C, 5·12% H, 7·45% N, 35·10% O. CD spectrum in acetonitrile (λ, nm ($\Delta\varepsilon$)): 241 sh (+1·42), 235 (+1·62), 219 (+1·25), 213 sh (+0·82), 192 (+2·9). Enantiomer (*S*)-(−)-*IX* was obtained from (*S*)-(+)-*VIII*; m.p. 185—186°C; $[\alpha]_D^{23}$ −40·8° (*c* 2; acetonitrile).

(±)-2-Ethoxycarbonyl-5-oxo-2-pyrrolidinepropanoic Acid (*X*) and (±)-Ethyl 2-Carboxy-5-oxo-2-pyrrolidinepropanoate (*XI*)

The racemic anhydride *IX* (18·3 g) was dissolved in ethanol (200 ml) by heating at 80°C for 30 min. The clear solution was evaporated and the residue dissolved in hot water (30 ml). The crystals, deposited after standing overnight in a refrigerator, were filtered (9·8 g) and the filtrate was evaporated under reduced pressure. The remaining mixture was chromatographed on a column of silica gel in the system *b*. The first fraction consisted of a small quantity of the diethyl ester *VII* (0·8 g; R_F (*b*) 0·70), the second one (4·5 g; R_F (*b*) 0·46) was found by thin layer chromatography to be identical with the above crystalline substance. The two crops of the latter were combined and crystallized from water to give 12·6 g (55%) of the monoethyl ester *X*, m.p. 122—123°C. For $C_{10}H_{15}NO_5$ (229·2) calculated: 52·40% C, 6·59% H, 6·11% N, 34·90% O, 19·65% C_2H_5O; found: 52·43% C, 6·53% H, 6·19% N, 35·02% O, 19·38% C_2H_5O; neutralization equivalent 227; pK_a: 4·53. IR spectrum (KBr, cm^{-1}): 3 600—2 360 (O—H), 3 195 (N—H), 1 730, 1 705, 1 645 (C=O). Mass spectrum (70 eV; *m/e* (relative intensity, %)): 184 (2), 156 (100), 138 (25).

The third fraction obtained by chromatography (6·3 g; R_F (*b*) 0·22) was also crystallized from water to give 5·5 g (24%) of the isomeric mono ester *XI*, m.p. 112—114°C. For $C_{10}H_{15}NO_5$ (229·2) calculated: 52·40% C, 6·59% H, 6·11% N, 19·65% C_2H_5O; found: 52·15% C, 6·85% H, 6·08% N, 19·50% C_2H_5O, neutralization equivalent 231; pK_a: 3·42. IR spectrum (KBr, cm^{-1}): 3 600—2 325 (O—H), 3 205 (N—H), 1 730, 1 635 (C=O). Mass spectrum (70 eV; *m/e* (relative intensity, %)): 184 (100), 156 (30), 138 (60), 128·0340 (16).

Optically Active Mono Esters *X* and *XI*.

The title compounds were prepared by the procedure described for the racemate. Starting from (*R*)-(+)-*IX* (6·4 g), the following two substances were obtained: (*R*)-(−)-*X* (3·6 g; 45%), m.p. 126−128°C; R_F (*b*): 0·46; $[\alpha]_D^{23}$ −9° (*c* 1; water). For $C_{10}H_{15}NO_5$ (229·2) calculated: 6·11% N; found: 6·28% N; neutralization equivalent 228. IR spectrum (KBr, cm^{-1}): 3 600−2 350 (O−H), 3 295 (N−H), 1 735, 1 705, 1 640 (C=O). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 212·5 (+4·75), 200 (0), 191 (−4·85). (*R*)-(−)-*XI* (1·7 g; 21%), m.p. 124−125°C; R_F (*b*) 0·22; $[\alpha]_D^{23}$ −18° (*c* 1; water). For $C_{10}H_{15}NO_5$ (229·2) calculated: 6·11% N; found: 6·05% N, neutralization equivalent 231. IR spectrum (KBr, cm^{-1}): 3 600−2 350 (O−H), 3 295 (N−H), 1 730, 1 635 (C=O). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 211 (+4·43), 201 (0), 193 (−4·43). The yields and the absolute values of the physical constants of (*S*)-(+)-*X* and (*S*)-(+)-*IX* obtained from (*S*)-(−)-*IX* are identical with those of their enantiomers.

Samples (10 mg) of both enantiomers of *X* and of those of *XI* were hydrolyzed with 1M-NaOH (1 ml) for 2 h, acidified with 1M-HCl (1·5 ml) and diluted with water to 10 ml each. A sample of (*R*)-(−)-*VIII* (10 mg) was subjected to the same procedure. CD spectra of solutions obtained by hydrolysis of the enantiomers of *X* and *XI* were, within the limits of the experimental errors of CD measurement, identical with, or mirror images of, that of the standard (*R*)-(−)-*VIII*.

(±)-Ethyl 1,7-Dioxo-2,8-diazabicyclo[4,3,0]nonane-9-carboxylate (*XIV*)

To a stirred solution of the racemic monoethyl ester *X* (2·29 g) in dichloromethane (25 ml) were added diphenyl phosphoroazidate (2·8 ml) and triethylamine (1·4 ml), and the mixture was stirred at room temperature for 5 h. Dichloromethane was then distilled off, the residue dissolved in toluene (20 ml) and heated at 80°C for 6 h. The solution was taken down under reduced pressure and the remaining oily substance dissolved in hot ethyl acetate (20 ml). The crystals, precipitated after standing for a day at room temperature, were collected and crystallized from ethyl acetate to yield 1·52 g (67%) of the bicyclic compound *XIV*, m.p. 188−189°C; R_F (*b*) 0·19, R_F (*c*) 0·44, R_F (*d*) 0·35. For $C_{10}H_{14}N_2O_4$ (226·2) calculated: 53·09% C, 6·23% H, 12·38% N, 19·92% C_2H_5O; found: 53·42% C, 6·30% H, 12·10% N, 19·60% C_2H_5O. IR spectrum (KBr, cm^{-1}): 3 220 (N−H), 1 760, 1 730, 1 665 (C=O). ^{1}H NMR spectrum ($CDCl_3$; δ, ppm): 1·31 (t, 3 H) and 4·28 (q, 2 H) for CH_3CH_2, 1·7−2·3 (m, 2 H) and 3·0−3·6 (m, 2 H) for (N)CH_2CH_2(C), 2·3−2·8 (m, 4 H) for (C)CH_2CH_2(C), 7·09 (br. s, 1 H), disappearing in D_2O, for NH.

The enantiomer (*R*)-(−)-*XIV* was prepared from (*R*)-(−)-*X* (0·93 g) by the same procedure as described above with the following modifications. The residue obtained after the evaporation of toluene was dissolved in chloroform (25 ml) and the solution was extracted with water (5 × 5 ml). The aqueous solution was evaporated under reduced pressure and the remaining oil dried in a vacuum desiccator (0·55 g). After triturating with cold ethyl acetate, it turned into a powder which was crystallized from hot ethyl acetate. The chromatographically pure (*R*)-(−)-*XIV* was obtained in 28% yield (260 mg), m.p. 142−143°C; R_F (*c*) 0·44; $[\alpha]_D^{23}$ −2·0 ± 0·5° (*c* 1;water). For $C_{10}H_{14}N_2O_4$ (226·2) calculated: 53·09% C, 6·23% H, 12·38% N; found: 52·95% C, 6·35% H, 12·25% N. IR spectrum (KBr, cm^{-1}): 3 280 (N−H), 1 755, 1 730, 1 655 (C=O). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 242 (−0·55), 237 (0), 220 (+8·21), 212 (0), 201 (−10·5), 188 (0), 185! (+4).

The enantiomer (*S*)-(+)-*XIV* was obtained from (*S*)-(+)-*X* (0·84 g), in the similar manner, in 24% yield; m.p. 141−142°C; $[\alpha]_D^{25}$ +2·0 ± 0·5° (*c* 1; water). CD spectrum in water (λ, nm ($\Delta\varepsilon$)): 246 (+0·53), 238 (0), 220·5 (−8·37), 211·5 (0), 202 (+10·3), 190·5 (0), 185! (−3).

Determination of Enantiomeric Purity of (*S*)-(+)-*XIV*

In the ^{1}H NMR spectrum of racemic *XIV*, recorded in the presence of increasing amounts of tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]europium (16·4 mg of (±)-*XIV* with 17, 28 and 34 mg of the reagent, respectively, in 0·3 ml of $CDCl_3$), a small downfield shift of the signals due to the methylene protons (see above) can be observed. Because of the complicated structures of the multiplets, however, their splitting cannot be seen clearly. In contrast, the NH proton signal is shifted very strongly with a pronounced separation of the signals belonging to the two enantiomeric components of the racemate (from δ 6·42 to 9·62 and 9·78 ($\Delta\delta$ 0·16), 11·43 and 11·74 ($\Delta\delta$ 0·31), and 12·18 and 12·62 ($\Delta\delta$ 0·44) in the three experiments, respectively). In an analogous experiment with (*S*)-(+)-*XIV* and the same amounts of the reagent, similar shifts of the NH proton signals were observed without any sign of its doubling. Taking into account the experimental sensitivity of the method, the enantiomeric purity of (*S*)-(+)-*XIV* is assumed to be at least 96%.

(±)-1,7-Diazaspiro[4,4]nonane-2,6-dione (*I*)

A) The diacid *VI* (0·5 g) had been heated to 190°C at 1·3 kPa till the decomposition ceased and then sublimed at 240°/13 Pa. Resublimation, followed by crystallization from methanol, afforded 242 mg (60%) of the product *I*, m.p. 246–248°C, identical with the compound, prepared by the procedure *B*).

B) A solution of the racemic bicyclic compound *XIV* (1·5 g) in azeotropic hydrochloric acid (20 ml) was heated in a sealed tube at 120°C for 10 h. The resulting solution was decolorized by charcoal and evaporated under reduced pressure. The hygroscopic solid residue was dried over KOH in a vacuum desiccator (2 g). According to thin layer chromatography and electrophoresis, the product contained about 90% of the ninhydrine positive substance *XV* of R_F (*e*) 0·31. Thionyl chloride (1·19 g) was added dropwise to cooled methanol (20 ml), and the solution was stirred for 20 min at −10°C. To this solution was added, under cooling and stirring, a methanolic solution of the crude dihydrochloride *XV* (2 g in 15 ml). The mixture was stirred for 1 h below 0°C, then allowed to warm up to room temperature and kept for 4 h between 40 and 60°C. The solution was evaporated under reduced pressure, the residue dissolved again in methanol and evaporated. The latter procedure was repeated several times to eliminate traces of hydrogen chloride. An amorphous solid substance (*XVI*; 1·96 g) was obtained; R_F (*e*) 0·56. For $C_9H_{20}Cl_2N_2O_4$ (291·3) calculated: 9·62% N, 21·31% OCH_3; found: 9·25% N, 21·90% OCH_3. It was dissolved in methanol (20 ml), the solution made alkaline (pH 8) with triethylamine and refluxed for 20 min on a water bath. The base was eliminated by treating the methanolic solution with Amberlite-15 cation exchange resin. After decolorizing with charcoal, the solution was evaporated and the remaining solid substance crystallized from ethanol and water to yield 0·39 g (38%) of the racemic spirodilactam *I*; m.p. 244–246°C. For $C_7H_{10}N_2O_2$ (154·2) calculated: 54·53% C, 6·54% H, 18·17% N; found: 54·25% C, 6·75% H, 18·37% N. IR spectrum (KBr, cm^{-1}): 3 240 (N—H), 1 715, 1 682 (C=O). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1·80–2·40 m, 6 H (3 × CH_2), 3·17 m, 2 H (N—CH_2), 7·69 broad, 1 H (NH), 7·86 broad, 1 H (NH). ^{13}C NMR spectrum (D_2O; δ, ppm): 30·76, 31·12, 34·77, 39·39, 65·83, 180·46, 182·67. Mass spectrum (70 eV; *m/e* (relative intensity, %)): 154 (M^+, 100), 136 (40), 125 (40), 109 (100), 97 (70).

(*R*)-(+)-*I*. From (*R*)-(−)-*XIV* (170 mg) 35 mg (28%) of (*R*)-(+)-*I* was obtained by an analogous procedure as described for the racemate; m. p. 280–282°C; $[\alpha]_D^{25}$ +63° (*c* 1; water). For $C_7H_{10}N_2O_2$ (154·2) calculated: 18·17% N; found: 18·32% N. IR spectrum (KBr, cm^{-1}): 3 235 (N—H), 1 712, 1 680 (C=O). CD spectra (λ, nm ($\Delta\varepsilon$)) in water: 219 (+6·82), 205 sh (+4·30), 193 (+0·3) min, 180! (+8); in acetonitrile: 228·5 (+6·53), 215 sh (+2·99), 204·5 (0), 197·5 (−4·0), 191 (0), 181! (+5).

(*S*)-(−)-*I*. Yield and scalar values of physical constants were identical with those of the enantiomer. $[\alpha]_D^{25}$ −63° (*c* 1; water). CD spectra (λ, nm ($\Delta\varepsilon$)) in water: 219·5 (−6·70), 205 sh (−4·35), 193 (−0·6) min, 180! (−9); in trifluoroethanol: 219·5 (−7·48), 205 sh (−4·39), 192 (0), 180! (−4); in ethanol: 224 (−6·32), 210 sh (−3·46), 202 (0), 195·5 (+3·0), 188 (0) 185! (negative).

Partial Optical Resolution of the Racemic Dilactam *I*

Racemic dilactam *I* (130 mg) in water (1 ml) was applied on a column of triacetylcellulose (40 g; 70 × 1·4 cm). Elution with water (1 ml fractions) afforded 11 mg of material with negative Cotton effect, 94 mg of inactive material and 10·3 mg of compound with positive Cotton effect. Several chromatographies were performed, the total amount of starting optically inactive material being 1·4 g. Fractions, exhibiting negative Cotton effect were combined (total 160 mg) and chromatographed on the same column under the same conditions, affording 30·6 mg of the enriched compound. Third chromatography of this material afforded a fraction (5·3 mg) which was used in the CD measurements and had about 30% optical purity.

(±)-N,N-Bis-nitroso-1,7-diazaspiro[4,4]nonane (*XIX*)

Racemic *I* (100 mg) was suspended in benzene (5 ml) and a solution of Red-Al (sodium bis(2--methoxyethoxy)dihydridoaluminate; 0·80 g) in benzene (5 ml) was added dropwise to it at 40°C in 30 min. During the addition of the reagent evolution of hydrogen was observed. The mixture was refluxed for 5 h and then poured into a 20% aqueous NaOH solution (25 ml). The phases were separated and the benzene solution was extracted with 20% aqueous NaOH solution (5 ml), water (2 × 10 ml) and 1M-HCl (2 × 5 ml). The aqueous phases were combined (about 60 ml) and distilled until the pH of the condensing distillate, after reaching a maximum, dropped again to 8. The distillate (pH 11) was acidified with 0·25M-HCl to pH 2 (4·2 ml) and evaporated. The residue was several times dissolved in ethanol and evaporated. Finally it was dried in a desiccator over P_2O_5 and KOH to yield the hygroscopic dihydrochloride of 1,7-diazaspiro[4,4]nonane (*XVIII*; 90 mg). For $C_7H_{16}Cl_2N_2$ (199·2) calculated: 14·06% N, 35·64% Cl^-; found: 13·52% N, 34·85% Cl^-. IR spectrum (KBr, cm^{-1}): 3 100–2 300, 15 92 (NH_2^+).

The above dihydrochloride (70 mg) was dissolved in water (2 ml), acidified with 6M-HCl to pH 2 and warmed to 90°C. To this hot solution sodium nitrite (80 mg) dissolved in water (0·5 ml) was added in 3 portions, and the heating was continued for 1 h. The solution was extracted with chloroform (5 × 3 ml) and the organic phase dried ($MgSO_4$) and evaporated to afford 32 mg of the N,N-bis-nitroso derivative *XIX*; m.p. 81–82°C. For $C_7H_{12}N_4O_2$ (184·2) calculated: 45·64% C, 6·57% H, 30·42% N; found: 45·43% C, 6·72% H, 29·95% N. IR spectrum (KBr, cm^{-1}): 1 410, 1 330, 1 315 (N—N=O, dimer). UV spectrum in ethanol (λ, nm (ε)): 355 (193).

(*R*)-(−)-*XIX*. Prepared according to the above-described procedure starting from (*R*)-(+)-*I* (25 mg); yield 6 mg; m.p. 103–105°C. UV spectrum in ethanol (λ, nm (ε)): 355 (186). CD spectrum in ethanol (λ, nm ($\Delta\varepsilon$)): 367·5 (−0·12), 246·5 (−10·8), 233 (0), 218·5 (+8·1).

(*S*)-(+)-*XIX*. From (*S*)-(−)-*XVII* (ref.[4]) (35 mg) the (*S*)-(+)-enantiomer of *XIX* (10 mg) was prepared by an analogous way; m.p. 102–103°C. UV spectrum in ethanol (λ, nm (ε)): 355 (180). CD spectrum in ethanol (λ, nm ($\Delta\varepsilon$)): 367 (+0·10), 246·5 (+11·2), 232 (0), 218 (−7·5).

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