SYNTHESIS AND ABSOLUTE CONFIGURATION OF THREE ISOMERIC SPIRO-BIS(2-PYRROLIDINONES)*

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Syntheses are described for three isomeric spiro-bis-(2-pyrrolidinones): 2,7-diazaspiro[4,4]nonane--3,8-dione (*II*), 2,7-diazaspiro[4,4]nonane-1,8-dione (*IV*) and 1,7-diazaspiro[4,4]nonane-2,8-dione (*VI*). All the syntheses were carried out starting from 3-carboxy-5-oxo-3-pyrrolidineacetic acid (*VIII*) of known configuration, allowing the assignation of absolute configuration to compounds *II*, *IV* and *VI* synthesized through stereochemically unequivocal reaction steps.

As it has been revealed by the pioneering work of Moffitt[1], the optical activity of polypeptides and proteins is principally due to the peptide groups held in a more or less fixed position with respect to one another by the whole molecular framework. The rotatory strengths of electronic transitions in the inherently achiral amide chromophores result from the interaction of these groups with one another and with their nonchromophoric but chiral environment. Therefore, optical activity of molecules containing two or more amide groups depends very sensitively on the relative arrangement of these chromophores. In the knowledge of the correlation between, on the one hand, the signs and intensities of the CD bands assigned to the electronic transitions of the amide chromophores and, on the other, the relative orientation of the latter, valuable information can be obtained on the conformation of polyamides by investigating their chiroptical properties. For this aim many empirical and theoretical investigations have been done in the last decades[2]. From a theoretical point of view, the most outstanding of these have been the systematic calculations made by the group of Schellman[3].

By giving the rotatory strengths of both the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ transitions of the "diamide unit", *i.e.* of two amide chromophores connected through one carbon atom and fixed in all possible relative positions, these calculations may be regarded, in principle, as the complete solution of the problem. However, for the verification of their adequacy in providing correct values for the chiroptical parameters of diami-

* Part I of the series Spiro-bis(2-pyrrolidinones).

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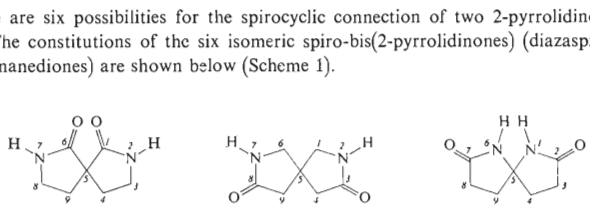
des, experimental investigations with a greater number of model compounds of various stereochemistry are required.

With the intention of a systematic experimental and theoretical study on the correlation of the chiroptical properties of diamides with the relative arrangement of the two amide chromophores, we tried to find simple model compounds having two fixed amide groups and lacking any other chromophoric moieties in their molecules. Due to their relatively rigid geometry, spirans built up to two 2-pyrrolidinone rings seem to be promising substrates for our investigations, so much the more, because the chiroptical properties of simple 2-pyrrolidinone derivatives have been very thoroughly studied by numerous authors[4-10].

There are six possibilities for the spirocyclic connection of two 2-pyrrolidinone rings. The constitutions of the six isomeric spiro-bis(2-pyrrolidinones) (diazaspiro-[4,4]nonanediones) are shown below (Scheme 1).



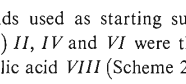
SCHEME 1

All the isomeric spiro-bis(2-pyrrolidinones) have chiral molecular structures. The enantiomers of *I*, *II* and *III* are of C_2 symmetry and seem to possess no center but an axis of chirality. However, the spiro carbon atom can be regarded, even in these constitutionally symmetric molecules, as the center of the so called spiro-chirality[11]. The specification according to the CIP conventions[11] of the absolute configuration of the C_2 symmetric spiro-bis(2-pyrrolidinones) *I*–*III* refers to the spiro carbon atom as a chiral center. In the molecules of the three other isomers (*IV*–*VI*), the spiro carbon atom represents a center of chirality.

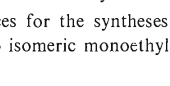
Of the six possible isomeric spiro-bis(2-pyrrolidinones), it is only the racemate of *III* for which a synthesis can be found in the literature[12]. A diphenyl derivative of *I*, 4,9-diphenyl-2,7-diazaspiro[4,4]nonane-1,6-dione, has also been prepared in racemic form[13].

In the present paper we report on the synthesis of three optically active spiro-bis-(2-pyrrolidinones): *II*, *IV* and *VI*. All of them contain the spiro carbon atom in position 4 of one of the pyrrolidinone rings and in positions 4, 3 or 5 of the other. The syntheses of all the three compounds were carried out starting from the same compound, 3-carboxy-5-oxo-3-pyrrolidineacetic acid (*VIII*) the absolute configuration of which has been deduced on the basis of an earlier work by Krow and Hill[14].

The compounds used as starting substances for the syntheses of the spiro-bis-(2-pyrrolidinines) *II*, *IV* and *VI* were the two isomeric monoethyl esters *X* and *XI* of the dicarboxylic acid *VIII* (Scheme 2).



VIIa: $R^1 = C_2H_5$ $R^2 = C_2H_5$
VIIb: $R^1 = CH_3$; $R^2 = CH_3$
VIII: $R^1 = H$; $R^2 = H$
X: $R^1 = H$; $R^2 = C_2H_5$
XI: $R^1 = C_2H_5$; $R^2 = H$



IX

SCHEME 2

The diethyl ester *VIIa* was prepared according to Krow and Hill[14] using ethyl chloroacetate instead of bromoacetate for the dialkylation of ethyl cyanoacetate. Krow and Hill[14] described the partial alkaline hydrolysis of *VIIa* as leading to a monoethyl ester (m.p. 127–129°C) to which they assigned, without any comment, structure *XI* (*III* in the cited paper[14]). However, the substance isolated by them has proved to be of structure *X* according to our experiments.

We have found that the hydrolysis of the diethyl ester *VIIa* with one equivalent of sodium hydroxide results in a mixture containing, according to TLC, both isomeric monoethyl esters *X* and *XI* together with about 10% of the unreacted diethyl ester *VIIa* and the same amount of the dicarboxylic acid *VIII*. A considerable amount (about 60%) of one of the two monoethyl esters crystallized out after the usual working-up of the hydrolysate. This substance (m.p. 129°C) proved to be identical with the product of Krow and Hill[14]. The remaining components of the hydrolysate were separated by column chromatography, after which also the other monoethyl ester could be obtained in pure form (m.p. 116°C). The proportion of the total amounts of the former and the latter half esters was found to be of about 2 : 3. These results are in apparent contradiction to those of Krow and Hill[14], because the monoethyl ester obtained by us in higher yield is not the product isolated or, at least, mentioned by them as the only one, but its isomer. Since the assignment of consti-

tution *XI* to the isolated monoethyl ester is not supported by any argument in the paper of Krow and Hill[14], a reexamination of the structures seemed to be necessary.

The correct constitutions of the two isomeric monoethyl esters isolated by us were determined by mass spectrometry. The base peaks found at *m/e* 128 (M − $CH_2COO.C_2H_5$) in the mass spectrum of the one substance (m.p. 129°C) and at *m/e* 156 (M − CH_2COOH) in that of the other (m.p. 116°C) allowed us to unambigously assign structure *X* to the former and structure *XI* to the latter.* These assignments have been indirectly supported also by ^1H and ^{13}C NMR spectroscopy providing an independent proof for the structure of *II* synthesized from the monoethyl ester *X*.

The mistake made by Krow and Hill with attributing the constitution of the more probable isomer *XI* to the less soluble product *X*, the only one they had isolated from the reaction mixture of the partial hydrolysis, however, does not in the least interfere with the correctness of the absolute configurations established by them in the cited paper[14].

Instead of the partial hydrolysis described by Krow and Hill[14], we developed a more convenient method for the transformation of *VIIa* into *X* and *XI*. The hydrolysis of the diethyl ester *VIIa* with more than two equivalents of alkali led to the dicarboxylic acid *VIII* as the only product. The latter was converted by treatment with acetic anhydride at 100°** into the intramolecular anhydride *IX* (Scheme 2). The ethanolysis of *IX* resulted in the mixture of *X* and *XI* (in a ratio of about 3 : 2) with quantitative yield. The isomeric monoethyl esters could be separated either by column chromatography as described above or by a more simple method based on the difference in solubility of the two half esters on the one hand, and of their dicyclohexylammonium salts, on the other.

The resolution of racemic *X* with quinine according to Krow and Hill[14] led to (−)-*X*. Several (8 − 10) recrystallizations of the quinine salt were necessary to obtain (−)-*X* in optically pure form. The (+)-enantiomer of *X* could be prepared by repeated crystallizations of the partially resolved substance isolated from the mother liquors. The enantiomers of monoethyl ester *XI* were prepared by subsequent resolutions of the racemate with both enantiomers of 1-(*p*-nitrophenyl)-2-amino-1,3-propanediol in ethanol. The less soluble of the diastereomeric salts was that made up of the (+)-acid and the (−)-base (and its enantiomer).

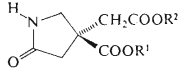
The alkaline hydrolysis of (−)-*X* and of (+)-*XI* led to (−)-*VIII* and (+)-*VIII*, respectively, with specific rotations of equal absolute values and of opposite signs. The

* In agreement with the proposed structures, the peak at *m/e* 156 is practically absent from the mass spectrum of isomer *X*, however, seemingly in contrast to them, a peak of lower intensity at *m/e* 128 does appear also in the spectrum of *XI*. The formation of the ion of mass 128 is due to a metastable transition (elimination of carbon monoxide) of a primary product (*m/e* 156) of the fragmentation of isomer *XI*.

** Under more vigorous conditions, *e.g.* by refluxing with acetic anhydride, also the amide nitrogen of the pyrrolidinone ring became acetylated.

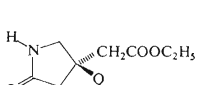
treatment of the latter with an excess of diazomethane gave (−)-*VIIb* and (+)-*VIIb*, respectively, the enantiomeric purity of which was found by ^{1}H NMR, using an optically active shift reagent, to be of min. 99%.

The absolute configuration of the monoethyl ester (−)-*X* has been established by Krow and Hill[14] to be *R*. (The erroneous constitution attributed to *X* does not invalidate the configuration assigned to its chiral center.) Thus, on the basis of the reactions described above, the configuration of the (−)-enantiomers of *VIIb*, *VIII* and *XI* must also be *R*.

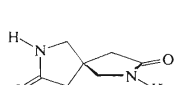


(−)-(*R*)-*VIIb*: $R^1 = CH_3$; $R^2 = CH_3$
(−)-(*R*)-*VIII*: $R^1 = H$; $R^2 = H$
(−)-(*R*)-*X*: $R^1 = H$; $R^2 = C_2H_5$
(−)-(*R*)-*XI*: $R^1 = C_2H_5$; $R^2 = H$

Synthesis of (+)-(R)-2,7-*diazaspiro*[4,4]*nonane*-3,8-*dione* ((+)-(R)-*II*): The ammonolysis of the non-isolated mixed anhydride prepared from *X* with isobutyl chloroformate in the presence of triethylamine led to the amide *XII* which was converted into the corresponding nitrile *XIII* using N,N-dimethyl-chloromethyleneiminium chloride as a dehydrating agent. The hydrogenation of *XIII* in the presence of a chromium containing Raney nickel catalyst under atmospheric pressure at room temperature led to the non-isolated amino ester *XIV*, whose subsequent spontaneous intramolecular acylation reaction resulted in the formation of *II*. The transformation of (−)-(*R*)-*X* yielded the (+)-enantiomer of 2,7-diazaspiro[4,4]nonane-3,8-dione (*II*), the *R* absolute configuration of which can be deduced from its synthesis (Scheme 3).



(−)-(*R*)-*X*: Q = COOH
(+)-(*R*)-*XII*: Q = CONH$_2$
(−)-(*R*)-*XIII*: Q = C≡N
(*S*)-*XIV*: Q = CH$_2$NH$_2$

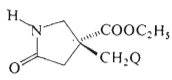


(+)-(*R*)-*II*

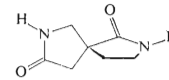
SCHEME 3

The synthesis of (+)-(R)-2,7-*diazaspiro*[4,4]*nonane*-1,8-*dione* ((+)-(R)-*IV*) was carried out through an analogous series of transformations starting from the monoethyl ester *XI*. The conversion of (+)-(*S*)-*XI* led to the formation of (+)-2,7-dia-

zaspiro[4,4]nonane-1,8-dione ((+)-*IV*), which must be, by following from its synthesis, of *R* absolute configuration (Scheme 4).



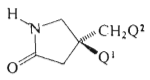
(+)-(*S*)-*XI*: Q = COOH
(+)-(*R*)-*XV*: Q = $CONH_2$
(+)-(*R*)-*XVI*: Q = C≡N
(*R*)-*XVII*: Q = CH_2NH_2

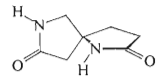


(+)-(*R*)-*IV*

SCHEME 4

Synthesis of (−)-(S)-1,7-*diazaspiro*[4,4]*nonane*-2,8-*dione* ((−)-(S)-*VI*): This isomer was also prepared from the monoethyl ester *X*. The strategy of the synthesis was the substitution of the carboxyl group by an amino group and the subsequent elongation of the acetic ester side chain by one methylene group, so that the ring closure of the resulting amino ester leads to the spiro compound *VI*. The first step in the series of reactions (Scheme 5) was a modified Curtius degradation[15]. The heating of a solution of *X*, diphenyl phosphoroazidate and triethylamine in tert-butyl alcohol resulted in the substitution of the carboxyl group of *X* by a tert-butyloxycarbonylamino group. The N-protected amino ester *XVIII* was hydrolysed by alkali to the carboxylic acid *XIX*, the side chain of which was elongated by Arndt–Eistert homologation. The N-protecting group of the homologated ester *XXI*, not isolated in pure form, was eliminated by acidolysis with trifluoroacetic acid. The spontaneous cyclization of the free amino ester *XXII*, liberated from its trifluoroacetate by triethylamine, resulted in the formation of *VI*. The synthesis starting from (−)-(*R*)-*X* led t (−)-*VI*. Since the Curtius degradation proceeds with retention of configuration[16], the absolute configuration of (−)-*VI* must be *S*.





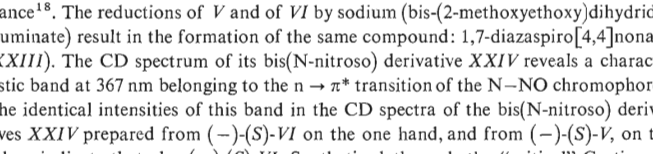
(−)-(*S*)-*VI*

(−)-(*R*)-*X*: Q^1 = COOH; Q^2 = $COOC_2H_5$
(−)-(*R*)-*XVIII*: Q^1 = NH—$COOC(CH_3)_3$; Q^2 = $COOC_2H_5$
(−)-(*R*)-*XIX*: Q^1 = NH—$COOC(CH_3)_3$; Q^2 = COOH
(*S*)-*XX*: Q^1 = NH—$COOC(CH_3)_3$; Q^2 = $COCHN_2$
(*S*)-*XXI*: Q^1 = NH—$COOC(CH_3)_3$; Q^2 = CH_2COOCH_3
(*S*)-*XXII*: Q^1 = NH_2; Q^2 = CH_2COOCH_3

SCHEME 5

The structures of the three isomeric spiro-bis(2-pyrrolidinones) are supported also by the IR, ^1H and ^{13}C NMR, and mass spectra. A comparative analysis of the spectroscopic data of all the six isomeric spiro-bis(2-pyrrolidinones) will be presented in another publication. The crystal and molecular structure of *II* has been determined also by X-ray diffraction[17].

The enantiomeric purity of (+)-(*R*)-*II* and of (+)-(*R*)-*IV* can be taken as granted, because that of the starting compounds (−)-(*R*)-*X* and (+)-(*S*)-*XI* was proved and the single steps of the syntheses did not interfere with the chiral centers of the intermediary compounds. It is only the spiro-bis(2-pyrrolidinone) *VI* the synthesis of which involves a substitution at the chiral center (*X* → *XVIII*). Though the Curtius degradation is known to proceed with retention of configuration[16], we wanted to furnish an independent proof concerning the enantiomeric purity of (−)-(*S*)-*VI*, too. In the course of our synthetic investigations on spiro-bis(2-pyrrolidinones), we also prepared the optically active 1,7-diazaspiro[4,4]nonane-2,6-dione (*V*) by a sequence of transformations not interfering with the chiral center of the optically pure starting substance[18]. The reductions of *V* and of *VI* by sodium (bis-(2-methoxyethoxy)dihydridoaluminate) result in the formation of the same compound: 1,7-diazaspiro[4,4]nonane (*XXIII*). The CD spectrum of its bis(N-nitroso) derivative *XXIV* reveals a characteristic band at 367 nm belonging to the n → π* transition of the N−NO chromophores. The identical intensities of this band in the CD spectra of the bis(N-nitroso) derivatives *XXIV* prepared from (−)-(*S*)-*VI* on the one hand, and from (−)-(*S*)-*V*, on the other, indicate that also (−)-(*S*)-*VI*. Synthetized through the "critical" Curtins degradation is optically pure. The details of the transformations summarized in Scheme 6 will be published[18] in connection with the synthesis of *V*.



(−)-(*S*)-*VI* (*S*)-*XXIII*: Q = H (*S*)-*XXIV*: Q = NO (−)-(*S*)-*V*

SCHEME 6

The CD data of the three spiro-bis(2-pyrrolidinones) described in this paper can be found in the Experimental. A detailed analysis of the chiroptical properties of 2-pyrrolidinone derivatives and of spiro-bis(2-pyrrolidinones), however, will be the subject of another publication.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Tottoli apparatus. Before microanalysis, the samples were dried in a vacuum desiccator over P_2O_5 for 8—10 h at a temperature adjusted

to the melting point of the substance in question. Thin-layer and column chromatography were made on silica gel (Kieselgel F_{254} DC-Fertigplatten and Kieselgel 60, resp.) using the following solvent mixtures: (*a*) ethyl acetate–pyridine–acetic acid–water (27 : 5 : 1·5 : 2·5); (*b*) ethyl acetate–pyridine–acetic acid–water (27 : 10 : 3 : 5); (*c*) ethyl acetate–pyridine–acetic acid–water (60 : 15 : 4·5 : 8); (*d*) chloroform–ethanol (4 : 1). The optical rotations were measured with a Zeiss Polamat instrument. IR, ^1H and ^{13}C NMR, mass and CD spectra were recorded on Zeiss IR-75, Varian XL-100, AEI MS 902 and Roussel-Jouan Dichrograph N° III (Jobin-Yvon) instruments, respectively.

(±)-3-Carboxy-5-oxo-3-pyrrolidineacetic Acid (*VIII*)

A suspension of *VIIa* (ref.[14]; 121·5 g, 0·5 mol) in 3M-NaOH (500 mol, 1·5 ml) was shaken for 2 h. The resulting solution was passed through a column filled with Amberlite IR-120 ion exchanger (H^+ cycle; about 3 l). The resin was washed with water until the eluate became neutral (pH 6). After evaporation of the eluate under reduced pressure, an oil (85 g, 90%) remained. Crystallization of the crude product from water (250 ml) afforded 73 g (78%) of the acid *VIII*, m.p. 168–170°C. For $C_7H_9NO_5$ (187·2) calculated: 44·92% C, 4·84% H, 7·48% N; found: 45·12% C, 5·03% H, 7·51% N. IR spectrum (KBr, cm^{-1}): 3 220 (N—H), 1 735, 1 720, 1 665 (C=O).

(±)-3-Carboxy-5-oxo-3-pyrrolidineacetic Anhydride (*IX*)

The acid *VIII* (50 g, 0·27 mol) was added in one portion to hot (100°C) acetic anhydride (500 ml), and the mixture was shaken in a boiling water bath for 10 min. The clear solution was cooled to 40°C and evaporated under reduced pressure (100–200 Pa). The procedure was repeated with preheated acetic anhydride (250 ml). The crystalline substance, remaining after evaporation of the solvent, was triturated several times with anhydrous ether (500 ml), collected on filter and dried in a vacuum desiccator over concentrated H_2SO_4. This crude product (45 g, 98%) was used in the next step. For analysis, a sample was recrystallized from acetonitrile; m.p. 181–183°C. For $C_7H_7NO_4$ (169·1) calculated: 49·70% C, 4·17% H, 8·28% N, 37·83% O; found: 49·95% C, 4·08% H, 8·25% N, 37·79% O. IR spectrum (KBr, cm^{-1}): 3 205 (N—H), 1855, 1 770, 1 685 (C=O).

(±)-Ethyl 3-Carboxy-5-oxo-3-pyrrolidineacetate (*X*) and (±)-3-(Ethoxycarbonyl)-5-oxo-3-pyrrolidineacetic Acid (*XI*)

A solution of the anhydride *IX* (33·8 g, 0·2 mol) in ethanol (500 ml) was refluxed for 2 h and evaporated under reduced pressure. The residue was dissolved in hot water (50 ml), cooled and inoculated with *X*. The crystals formed after standing at 5°C for 1 day were collected, washed with cold water (2 × 15 ml) and dried to yield 14 g (32·5%) of chromatographically pure *X*. For analysis, a sample was recrystallized from water; m.p. 129–131°C (ref.[14] m.p. 127–129°C). For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N, 37·17% O; found: 50·00% C, 6·16% H, 6·49% N, 37·32% O. IR spectrum (KBr, cm^{-1}): 3 295, 3 240 (N—H), 1 725, 1 665 (C=O). Mass spectrum (70 eV; *m/e* (relative intensity, %)): 215 (M^+, 5), 170 (45), 156(1), 128 (100).

The mother liquor was evaporated and the residue (30 g) dissolved in methanol (45 ml). To this solution were added dicyclohexylamine (27·5 g, 0·14 mol) and ether (100 ml), and the mixture was kept at 5°C for 2 days. The precipitate was collected and crystallized from methanol–ether (1 : 2) to yield 28 g (35%) of dicyclohexylammonium salt of *XI*, m.p. 149–151°C. For $C_{21}H_{36}N_2O_5$ (396·5) calculated: 63·60% C, 9·15% H, 7·07% N; found: 63·41% C, 9·23% H, 6·84% N.

The above dicyclohexylammonium salt (27 g, 68 mmol) was dissolved by shaking in a mixture of 10% aqueous Na_2CO_3 (100 ml) and ether (100 ml). The aqueous layer was washed with ether

(5 × 40 ml) and acidified with 6M-HCl (32 ml) to pH 2. Water was removed by distillation under reduced pressure and the residue triturated with ethanol (100 ml) to dissolve the monoethyl ester *XI*. The remaining NaCl was filtered off and the solution evaporated. Crystallization of the residue from acetonitrile yielded 11·8 g (81%) of chromatographically pure *XI*, m.p. 116–118°C. For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N, 37·17% O; found: 50·48% C, 6·34% H, 6·59% N, 36·93% O. IR spectrum (KBr, cm^{-1}): 3 240 (N—H), 1 730, 1 655, 1 630 (C=O). Mass spectrum (70 eV; *m/e* (relative intensity, %)): 215 (M^+, 3), 170 (22), 156 (100), 128 (30; metastable peak).

By evaporating the mother liquours of the dicyclohexylammonium salt and treating the residue with aqueous Na_2CO_3 and ether as described above, a mixture of *X* and *XI* was obtained. This was combined with the residues of the mother liquors of crystallization of *X* and *XI*. The mixture (16 g) was chromatographed on a column of silica gel using the mixture *a* as eluant. The first fractions contained pure *XI*, middle fractions a mixture of *X* and *XI*, and the last ones pure *X*. Chromatography of the middle fractions yielded some further amounts of *X* and *XI* in pure state. The isolated substances were finally crystallized from water or acetonitrile to yield additional crops of 5·6 g of *X* and 3·5 g of *XI*. The overall yields of *X* and *XI* were 19·6 g (45·6%) and 15·3 g (35·6%), respectively.

Resolution of Racemic *X*

A solution of racemic *X* (50 g, 0·23 mol) in ethanol (250 ml) was added to a hot ethanolic solution of anhydrous quinine (75 g, 0·23 mol in 500 ml). The crystals which separated after 12 h at 25°C were collected and repeatedly crystallized from the minimal amounts of ethanol. After each crystallization a 200 mg sample of the salt was decomposed (see below), and specific rotation of the liberated acid measured. A total of 10 crystallizations were necessary to obtain the quinine salt of optically pure (−)-(*R*)-*X* (30·3 g, 24%), m.p. 144–147°C. This salt was dissolved in a mixture of 10% aqueous $NaHCO_3$ (150 ml) and chloroform (100 ml), and the phases were separated. The aqueous phase was washed with chloroform (5 × 50 ml), acidified with 6M-HCl to pH 2 and evaporated under reduced pressure. The residue was triturated with anhydrous ethanol, the undissolved NaCl removed by filtration, and the solution evaporated. Crystallization of the residue (12 g) from water (30 ml) gave 10·2 g (20·4%) of optically pure (−)-(*R*)-*X*, m.p. 165–167°C, $[\alpha]_D^{25}$ −27·3° (*c* 2, water) (ref.[14] for a partially resolved sample: m.p. 153–156°C, $[\alpha]_D^{24}$ −22·3° (water)). For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N; found: 50·36% C, 6·26% H, 6·59% N; mol. wt. by titration: 214·5. IR spectrum (KBr, cm^{-1}): 3 255 (N—H), 1 730, 1 710, 1 640 (C=O).

The combined mother liquors of the resolution were evaporated, and the remaining quinine salt (95 g) was decomposed as described above. The recovered acid (38 g, $[\alpha]_D^{25}$ +8·5°) contained 31% of (+)-(*S*)-*X* and 69% of the racemate. The mixture was dissolved in hot water (100 ml), cooled and inoculated with *racemic X*. The crystals, separated after standing at 5°C for one day, were removed (22 g of racemic *X*), and the filtrate was concentrated to 40 ml and allowed to stand at room temperature for several hours. The mother liquor was decanted from the separated needle-shaped crystals which were rinsed with cold water (10 ml) and then crystallized from water (25 ml) to yield 6·4 g (12·8%) of (+)-(*S*)-*X*, m.p. 166–167°C, $[\alpha]_D^{25}$ +27·4° (*c* 2, water). For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N; found: 50·11% C, 6·21% H, 6·56% N. IR spectrum (KBr, cm^{-1}): 3 255 (N—H), 1 730, 1 710, 1 640 (C=O).

Resolution of Racemic *XI*

Racemic *XI* (21·5 g, 0·1 mol) dissolved in hot ethanol (60 ml) was added to a solution of (+)-1-(*p*-nitrophenyl)-2-amino-1,3-propanediol (21·1 g, 0·1 mol) in hot ethanol (400 ml). The crystals,

separated after standing for 2 days at 5°C, were collected and crystallized two times from ethanol (200 ml) giving 12 g (28%) of the salt of optically pure (−)-(*R*)-*XI*, m.p. 149—151°C. (The specific rotation of the acid, liberated from a sample of the salt, did not increase after the second crystallization.) A solution of this salt (12 g) in water (250 ml) was stirred with Amberlite IR-120 (H^+; 50 ml) for 1 h. The resin was filtered off, washed with water, and the combined filtrates were evaporated. The residue on crystallization from water (25 ml) gave 4·3 g (20%) of the optically pure (−)-(*R*)-*XI*, m.p. 156—157°C, $[\alpha]_D^{25}$ −33·7° (*c* 2, water). For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N; found: 50·49% C, 6·34% H, 6·70% N.

The combined mother liquors from the above resolution were evaporated and the remaining salt was decomposed by the procedure described above to yield partially resolved *XI* (12·6 g). Starting from this mixture, the whole resolution procedure was repeated, using (−)-1-(*p*-nitrophenyl)-2-amino-1,3-propanediol (12·3 g), to yield 14·2 g (33%) of the optically pure salt, m.p. 150—151°C. Decomposition of this salt and one crystallization of the product from water yielded 5·1 g (24%) of (+)-(*S*)-*XI*, m.p. 155—157°C, $[\alpha]_D^{25}$ +33·2° (*c* 2, water). For $C_9H_{13}NO_5$ (215·2) calculated: 50·23% C, 6·09% H, 6·51% N; found: 50·30% C, 6·27% H, 6·58% N.

Determination of Enantiomeric Purity of the Resolved Monoethyl Esters *X* and *XI*

A sample (200 mg) of (−)-(*R*)-*X* or (+)-(*S*)-*XI* was hydrolysed with 2M-NaOH (2 ml) for 2 h, acidified with 2M-HCl (2·5 ml) and diluted with water to 10 ml. The solutions had $[\alpha]_D^{25}$ −27·7° and +27·4°, respectively.

The two solutions were evaporated, the residues triturated with anhydrous ethanol, the undissolved NaCl removed by filtration, and the solutions concentrated to about 2 ml. The concentrates were heated with ethereal diazomethane (5 ml) and evaporated to give the two enantiomers of *VIIb* as oils; $[\alpha]_D^{25}$ −28·2° and +27·8° (*c* 2, methanol) for (−)-(*R*)- and (+)-(*S*)-*VIIb*, respectively.

The optical purity of the enantiomers of *VIIb* was determined by lanthanide-induced shift. First the ^1H NMR spectrum of the racemic *VIIb* (prepared from racemic *VIII* with ethereal diazomethane) was recorded in $CDCl_3$; δ, ppm: 2·64 (J_{AB} = 17, δ_{AB} = 32 Hz, 2 H), 2·87 (s, 2 H), 3·62 (J_{AB} = 10·5, δ_{AB} = 29 Hz, 2 H), 3·68 (s, 3 H), 3·77 (s, 3 H), 7·35 (br.s, 1 H). In the spectrum of a $CDCl_3$ solution, containing equal quantities (50 mg) of racemic *VIIb* and of tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-(+)-camphorato]europium (Merck), all the signals were doubled and shifted downfields (except the signal of the NH proton, the shift of which is very small and upfield). The lanthanide-induced shift and the doubling of the narrow singlets of the two methyl groups could be best measured. These signals found at 3·68 and 3·77 ppm in the spectrum of pure racemic *VIIb* appeared, in the presence of the shift reagent, at 3·85, 3·90, 3·97 and 4·02 ppm. Spectra of the single enantiomers of *VIIb*, taken in the presence of the same amount of the shift reagent, exhibited shifts of similar magnitude but without trace of any doubling. The two methyl singlets appeared at 3·90 and 3·97 ppm in the spectrum of (+)-*VIIb* and at 3·85 and 4·02 ppm in that of (−)-*VIIb*. Based on the sensitivity of the measurement, an enantiomeric purity of min. 99% can be estimated for both enantiomers of *VIIb*.

(+)-(*R*)-Ethyl 3-(Aminocarbonyl)-5-oxo-3-pyrrolidine Acetate ((+)-(*R*)-*XII*)

A solution of (−)-(*R*)-*X* (4·3 g, 20 mmol) in dimethylformamide (4 ml) was diluted with tetrahydrofuran (40 ml) and, after addition of triethylamine (3.9 ml, 28 mmol), cooled to −20°C. To this solution isobutyl chloroformate (3·9 ml, 28 mmol) dissolved in cold tetrahydrofuran (8 ml) was added dropwise. After 15 min of stirring at −20°C, a cold solution of ammonia (0.68 g,

40 mmol) in tetrahydrofuran (40 ml) was added. The mixture was stirred for 30 min at 0°C and for 1 h at room temperature. The seaprated triethylammonium chloride was removed by filtration and the solution evaporated. The residue was dissolved in water (50 ml), the solution washed with ethyl acetate (4 × 20 ml) and treated with Amberlite IR-120 (H^+ cycle; 20 ml). The substance, obtained after the evaporation of water, was found by TLC to be contaminated with some unreacted *X*. It was purified by chromatography on a column of silica gel in the solvent mixture *d*. The fractions containing only the amide *XII* were evaporated, the residue was dissolved in water (25 ml), treated with a small amount of charcoal and evaporated again to yield 2·3 g (54%) of chromatographically pure (+)-(*R*)-*XII* in the form of a colourless, viscous oil which could not be induced to crystallization and, therefore, was used in this form in the next step; $[\alpha]_D^{25}$ +9·5° (*c* 1, ethanol). IR spectrum (neat, cm^{-1}): 3 310, 3 205 (N—H), 1 730, 1 665 (C=O).

(−)-(*R*)-Ethyl 3-Cyano-5-oxo-3-pyrrolidine Acetate ((−)-(*R*)-*XIII*)

A solution of phosgene (1·5 g, 15 mmol) in tetrachloromethane (8 ml) was added dropwise to a cooled and stirred solution of dimethylformamide (1·15 ml, 15 mmol) in chloroform (30 ml) under vigorous evolution of CO_2. The stirring was continued for 30 min at 0°C and for 1 h at temperature. The solution of N,N-dimethyl-chloromethyleneiminium chloride, prepared in this way, was cooled to 0°C and added to a cold solution of (+)-(*R*)-*XII* (2·14 g, 10 mmol) in dimethylformamide (25 ml). After standing for 30 min at 0°C and 2 h at room temperature, the solution was evaporated and the remaining oil purified by chromatography on a column of silica gel, using the solvent mixture *d* as eluant. The isolated solid substance gave, after crystallization from water (12 ml), 1·22 g (62%) of (−)-(*R*)-*XIII*, m.p. 131—132°C, $[\alpha]_D^{25}$ −23·8° (*c* 2, water). For $C_9H_{12}N_2O_3$ (196·2) calculated: 55·09% C, 6·16% H, 14·28% N; found: 55·24% C, 6·40% H, 14·26% N. IR spectrum (KBr, cm^{-1}): 3 185 (N—H), 2 235 (C≡N), 1 725, 1 705 (C=O).

(+)-(*R*)-2,7-Diazaspiro[4,4]nonane-3,8-dione ((+)-(*R*)-*II*)

A solution of (−)-(*R*)-*XIII* (1·0 g, 5 mmol) in ethanol (25 ml) was hydrogenated over a Raney nickel catalyst containing chromium (0·5 g) under atmospheric pressure at room temperature for 8 h. After filtration, the catalyst was washed with water, the combined filtrate and washings were evaporated, the residue was taken up in water (25 ml) and the solution washed with ethyl acetate (3 × 10 ml). The solid substance, remaining after evaporation of the aqueous solution, was crystallized from ethanol (10 ml) to give 350 mg (45%) of (+)-(*R*)-*II*, m.p. 258—260°C, $[\alpha]_D^{25}$ +5·8° (*c* 1, water).

For $C_7H_{10}N_2O_2$ (154·2) calculated: 54·53% C, 6·54% H, 18·17% N, 20·75% O; found: 54·23% C, 6·78% H, 17·97% N, 20·95% O. IR spectrum (KBr, cm^{-1}): 3 220, 3 100 (N—H), 1 735, 1 690, 1 665 (C=O). ^{1}H NMR spectrum (dimethylsulfoxide-d_6; δ, ppm): 2·25 (br.s, 4 H), 3·23 (br.s, 4 H). 7·60 (br.s, 2 H). ^{13}C NMR spectrum (D_2O; δ, ppm): 42·92, 43·66, 54·32, 180·27. Mass spectrum (70 eV; *m/e* (relative intensity, %): 154 (M^+, 80), 112(25), 97(40), 96(100). CD spectrum (water; λ, nm (Δε)): 218 (+0·49), 197·5 (+3·22), 190(0), 181!(−3·14).

(+)-(*R*)-3-(Ethoxycarbonyl)-5-oxo-3-pyrrolidineacetamide ((+)-(*R*)-*XV*)

To a solution of (+)-(*S*)-*XI* (2·9 g, 13·5 mmol) and N-methylmorpohline (1·81 ml, 16·2 mmol) in a mixture of dimethylformamide (8 ml) and tetrahydrofuran (35 ml) cooled to −5°C was added isobutyl chloroformate (2·26 ml, 16·2 mmol) under stirring. The mixture containing the precipitated hydrochloride, was stirred for 10 min under cooling and then a cold solution of ammonia (0·34 g, 20 mmol) in tetrahydrofuran (17 ml) was added. After stirring for 1 h at −10°C,

a second portion of the ammonia solution (5 ml, 6 mmol) was added and stirring was continued for 4 h at room temperature. The precipitated salt was removed by filtration and the filtrate concentrated under reduced pressure. The residue was taken up in water (20 ml) and stirred with Dowex-50 (H^+-cycle; 5 ml) for 2 h. The resin was filtered out, washed several times with water, and the combined solutions were evaporated. The residue (2·6 g) was purified by chromatography on a column of silica gel (solvent mixture *d*). The isolated substance was crystallized from ethanol (10 ml) to give 1·9 g (66%) of pure (+)-(*R*)-*XV*, m.p. 135–136°C, $[\alpha]_D^{25}$ +22·3° (*c* 1, water). For $C_9H_{14}N_2O_4$ (214·2) calculated: 50·46% C, 6·58% H, 13·07% N; found: 50·21% C, 6·70% H, 13·27% N. IR spectrum (KBr, cm^{-1}): 3 245 (N—H), 1 730, 1 666, 1 630 (C=O).

(+)-(*R*)-3-(Ethoxycarbonyl)-5-oxo-3-pyrrolidineacetonitrile ((+)-(*R*)-*XVI*)

To a solution of (+)-(*R*)-*XV* (1·8 g, 8·4 mmol) in dimethylformamide (15 ml) cooled to 0°C was added a solution of N,N-dimethyl-chloromethyleneiminium chloride (12 mmol) in chloroform (30 ml) (see compound *XIII*). The mixture was allowed to stand for 2 h at room temperature, then a few drops of water were added and the solution was evaporated under reduced pressure. The residue was taken up in water (30 ml), the solution saturated with solid $KHCO_3$ (pH 9) and the nitrile *XVI* was extracted with ethyl acetate (6 × 20 ml). The extracts were dried (Na_2SO_4) and evaporated to yield 1·5 g (91%) of (+)-*XVI* as an oil which was pure by TLC ($R_F(d) = 0·8$), but could not be crystallized. $[\alpha]_D^{25}$ +14·2° (*c* 1, ethanol). IR spectrum (KBr, cm^{-1}): 3 350, 3 230 (N—H), 2 245 (C≡N), 1 730, 1 695 (C=O).

(+)-(*R*)-2,7-Diazaspiro[4,4]nonane-1,8-dione ((+)-(*R*)-*IV*)

A solution of the nitrile (+)-(*R*)-*XVI* (1·4 g, 7·2 mmol) in ethanol (60 ml) was hydrogenated over a chromium containing Raney nickel catalyst (0·3 g) under atmospheric pressure at room temperature. In the first 12 h, the solution took up about 60% of the calculated amount of hydrogen. Then a new portion of catalyst (0·3 g) was added and the hydrogenation continued for 10 h, until the uptake of hydrogene stopped (85% of the calculated amount). The catalyst was removed by filtration and washed with water. The residue obtained after evaporation of the combined filtrates showed several impurities on TLC. It was purified by chromatography on a column of silica gel (solvent mixture *a*). After evaporation of fractions showing only the expected spot on TLC ($R_F(a) = 0·35$), a solid residue was obtained which was crystallized from methanol–ether to yield 165 mg (15%) of the chromatographically pure (+)-(*R*)-*IV*. m.p. 143°C (dec), $[\alpha]_D^{25}$ +7·5° (*c* 1, water). For $C_7H_{10}N_2O_2$ (154.2) calculated: 54·53% C, 6·54% H, 18·17% N, found: 54·35% C, 6·80% H, 17·95% N. IR spectrum (KBr, cm^{-1}): 3 225 (N—H), 1 690, 1 660 (C=O). ^{13}C NMR spectrum (D_2O; δ, ppm): 35·42, 40·39, 40·58, 47·66, 51·69, 179·59, 182·24. Mass spectrum (70 eV; *m/e* (relative intensity, %)): 154(M^+, 35), 126(60), 112(100), 98(40), 97(50). CD spectrum (water; λ, nm ($\Delta\varepsilon$)): 213(+1·74), 207(0), 199(−4·51), 191·5(0), 186·5(+2·20), 182!(0).

(−)-(*R*)-Ethyl 3-(Tert-butyloxycarbonylamino)-5-oxo-3-pyrrolidineacetate ((−)-(*R*)-*XVIII*)

To a suspension of (−)-(*R*)-*X* (5·0 g, 23·3 mmol) in tert-butyl alcohol (55 ml) were added triethylamine (3·3 ml, 23·3 mmol) and diphenyl phosphoroazidate (10·2 g, 31 mmol). The mixture was refluxed for 36 h and then evaporated under reduced pressure (100–200 Pa). The residue was dissolved in ethyl acetate (100 ml), washed with 10% aqueous Na_2CO_3 solution (5 × 30 ml) and 10% aqueous NaCl solution (30 ml), dried (Na_2SO_4) and evaporated. The residue was crystallized from a mixture of ethyl acetate and hexane to yield 1·81 g (27%) of (−)-(*R*)-*XVIII*, m.p.

111–113°C, $[\alpha]_D^{25}$ −20·3° (*c* 1, ethanol). For $C_{13}H_{22}N_2O_5$ (286·3) calculated: 54·53% C, 7·75% H, 9·78% N; found: 54·28% C, 8·03% H, 9·96% N. IR spectrum (KBr, cm^{-1}): 3 395, 3 200 (N—H), 1 730, 1 710, 1 695 (C=O).

(−)-(*R*)-3-(Tert-butyloxycarbonylamino)-5-oxo-3-pyrrolidineacetic Acid ((−)-(*R*)-*XIX*)

(−)-(*R*)-*XVIII* (1·5 g, 5·2 mmol) was dissolved in 0·5M NaOH (13 ml, 6·5 mmol) and stirred for 2 h at room temperature. The mixture was neutralized with 2M HCl to pH 6, concentrated under reduced pressure to about a half of its volume, acidified with 2M-HCl to pH 3·5, saturated with NaCl (about 1·5 g), and extracted with ethyl acetate (4 × 10 ml). Evaporation of the extracts and crystallization of the residue from ethyl acetate–hexane furnished 1·05 g (78%) of the chromatographically pure (−)-(*R*)-*XIX*, m.p. 169–170°C, $[\alpha]_D^{25}$ −21·6° (*c* 1·3, ethanol). For $C_{11}H_{18}N_2O_5$ (258·3) calculated: 51·15% C, 7·02% H, 10·84% N; found: 51·32% C, 7·19% H, 10·97% N; molecular weight by titration: 255. IR spectrum (KBr, cm^{-1}): 3 375, 3 335 (N—H), 1 725, 1 685, 1 645 (C=O).

(−)-(*S*)-1,7-Diazaspiro[4,4]nonane-2,8-dione ((−)-(*S*)-*VI*)

Isobutyl chloroformate (0·70 ml, 5 mmol) was added dropwise to a cooled (−5°C) and stirred solution of (−)-(*R*)-*XIX* (1·03 g, 4·0 mmol) and triethylamine (0·70 ml, 5 mmol) in a mixture of dimethylformamide (3 ml) and tetrahydrofuran (18 ml). The mixture was stirred at −5°C for 30 min, then an excess of ethereal diazomethane (25 ml, about 25 mmol) was added, and the stirring was continued for 2 h at 0°C and for 3 h at room temperature. After standing overnight, the mixture was filtered and the filtrate evaporated under reduced pressure. The remaining oil was dissolved in ethyl acetate (40 ml), washed with 10% aqueous $KHCO_3$ solution (2 × 10 ml) and saturated aqueous NaCl solution (2 × 10 ml), dried (Na_2SO_4) and evaporated. The diazoketone *XX*, obtained (oil, 1·3 g), was found to be pure on TLC ($R_F(d) = 0·5$). IR spectrum (KBr, cm^{-1}): 2 105 (NN).

To a solution of the crude diazoketone *XX* (1·3 g) in methanol (25 ml) was added a methanolic suspension of Ag_2O prepared from $AgNO_3$ (0·77 g). After refluxing for 2 h, the mixture was set aside overnight. The precipitate was removed by repeated filtration through a bed of charcoal, and the solution was evaporated under reduced pressure. The remaining oil (1·0 g) was dried in a vacuum desiccator over P_2O_5. It was pure on TLC ($R_F(d) = 0·6$); the band at 2 105 cm^{-1} disappeared from its IR spectrum.

This ester *XXI* was dissolved in trifluoroacetic acid (10 ml), allowed to stand for 1 h, and the solvent was removed under reduced pressure. The remaining oil was triturated with ether (2 × × 20 ml) to turn into a solid which was dried in a vacuum desiccator over P_2O_5 and KOH. The trifluoroacetate of the amino ester *XXII* was found to be pure on TLC (R_F (*d*) = 0·1). It was dissolved in methanol (20 ml), and after addition of N-methylmorpholine (2·2 ml; pH 8) the solution was allowed to stand overnight. The oil remaining after the evaporation of the solvent was found on TLC to be a mixture of several components. It was purified by repeated chromatography on a column of silica gel (solvent mixture *c*). Evaporation of the fractions showing the expected spot on TLC ($R_F(a) = 0·35$) yielded, after crystallization from ethanol–ether, 110 mg (17%) of (−)-(*S*)-*VI*, m.p. 160–162°C, $[\alpha]_D^{25}$ −0·5°, $[\alpha]_{366}^{25}$ −7·5° (*c* 1, water). For $C_7H_{10}N_2O_2$ (154·2) calculated: 54·53% C, 6·54% H, 18·17% N; found: 54·45% C, 6·70% H, 18·05% N. IR spectrum (KBr, cm^{-1}): 3 460, 3 210 (N—H), 1 690, 1 660 (C=O). ^{13}C NMR spectrum (D_2O; δ, ppm): 31·05, 33·40, 44·13, 55·35, 63·97, 179·23, 181·55. Mass spectrum (70 eV; *m/e* (relative intensity, %)): 154(M^+, 100), 97(50). CD spectrum (water; λ, nm (Δε)): 195(−4·1), 180!(0).

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