SYNTHESIS OF OPTICALLY ACTIVE 4,4- AND 5,5-DISUBSTITUTED 4,5-DIHYDRO-6*H*-CANTHIN-6-ONES AND THEIR CD SPECTRA* ** ***

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Synthesis of several optically active 4,4- and 5,5-disubstituted 4,5-dihydro-6*H*-canthin-6-ones ((*R*)-(+)-*VII*, (*S*)-(−)-*XII* and (*R*)-(+)-*XVIII*) and 5,5-disubstituted 4,5-dihydro-6*H*-canthin-4,6-diones ((*S*)-(−)-*XIX* and (*R*)-(+)-*XX*) is described and CD spectra of these compounds are discussed.

In our previous communications we have described the synthesis[1] of racemic 4,4- and 5,5-disubstituted derivatives of 4,5-dihydro-6*H*-canthin-6-one (*I*) and determination of the absolute configuration[2] of 2-allyl-2-ethyl-3-methoxycarbonylpropionic acid (*II*). These studies constitute a basis for synthesis of the title compounds of defined absolute stereochemistry. The present communication describes such synthesis, together with the CD spectra of the products.

The chiral 4,4-disubstituted 4,5-dihydro-6*H*-canthin-6-one *VII* was prepared starting from 2-ethyl-2-methyl-3-methoxycarbonylpropionic acid[1,3] (*III*) highly enriched in one antipode by crystallization of its dehydroabietylamine salt from methanol. The dextrorotatory ester–acid *III*, liberated from the dextrorotatory salt, was assigned the (*R*)-configuration because on treatment with diazomethane it was converted into (*R*)-(+)-dimethyl 2-ethyl-2-methylbutanedioate (*IV*). Its optical purity (83%) was determined by comparison with the optically pure[2] dimethyl ester (*S*)-(−)-*IV*. Using our previously described[1] method, we converted the acid (*R*)-(+)-*III via* the tryptamide (*R*)-(+)-*V* into the tetrahydro base (*R*)-(+)-*VI* which was dehydrogenated to give the oily (*R*)-(+)-4-ethyl-4-methyl-4,5-dihydro-6*H*-canthin-6-one (*VII*). Both enantiomers of another base of this group, (*R*)-(+)-*VIII* and (*S*)-(−)-*VIII*, were described by us already earlier[1,2].

Synthesis of 5,5-disubstituted bases started from the optically pure dimethyl butanedioates (*S*)-(−)-*IX* (ref.[2]) and (*R*)-(+)-*X* the latter of which was prepared by hydrogenation of the corresponding allyl derivative (*R*)-(−)-*XI* (ref.[2]). Both diesters were selectively saponified with 1·2 equivalent of hot methanolic sodium

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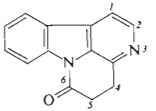
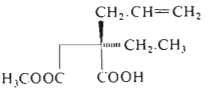
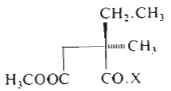
hydroxide to give the ester-acids (*S*)-(−)-*XII* and (*R*)-(+)-*XIII*. Since the planned preparation of the tryptamides from $N_{(b)}$-benzyltryptamine was not possible because of instability of the reaction product, including the isomeric amide *XIV*, we resorted



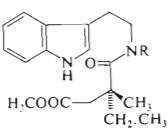
I



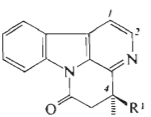
(*R*)-(−)-*II*



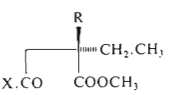
(*R*)-(+)-*III*, X = OH
(*R*)-(+)-*IV*, X = OCH_3



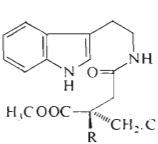
(*R*)-(+)-*V*, R = H
XIV, R = $C_6H_5CH_2$



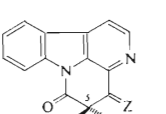
(*R*)-(+)-*VI*, $R^1 = CH_3$, $R^2 = C_2H_5$, 1,2-dihydro
(*R*)-(+)-*VII*, $R^1 = CH_3$, $R^2 = C_2H_5$
(*R*)-(+)-*VIII*, $R^1 = C_2H_5$, $R^2 = C_3H_7$
(*S*)-(−)-*VIII*, $R^1 = C_3H_7$, $R^2 = C_2H_5$



(*S*)-(−)-*IX*, R = CH_3, X = OCH_3
(*R*)-(+)-*X*, R = C_3H_7, X = OCH_3
(*R*)-(−)-*XI*, R = $CH_2CH{=}CH_2$, X = OCH_3
(*S*)-(−)-*XII*, R = CH_3, X = OH
(*R*)-(+)-*XIII*, R = C_3H_7, X = OH



(*S*)-(−)-*XV*, R = CH_3
(*R*)-(+)-*XVI*, R = C_3H_7



(*S*)-(−)-*XVII*, R = CH_3, Z = H_2
(*R*)-(+)-*XVIII*, R = C_3H_7, Z = H_2
(*S*)-(−)-*XIX*, R = CH_3, Z = O
(*R*)-(+)-*XX*, R = C_3H_7, Z = O

to the Schotten–Baumann method[1]. The acids (*S*)-(−)-*XII* and (*R*)-(+)-*XIII* afforded the corresponding glassy amide (*S*)-(−)-*XV* and the crystalline amide (*R*)-(+)-*XVI*, respectively, which were in the described manner[1] converted into the 5,5-dialkyl-4,5-dihydro-6*H*-canthin-6-ones (*S*)-(−)-*XVII* and (*R*)-(+)-*XVIII*, as well as into the 5,5-dialkyl-4,5-dihydro-6*H*-canthin-4,6-diones (*S*)-(−)-*XIX* and (*R*)-(+)-*XX*.

The CD spectra (taken on a Roussel–Jouan instrument*) of the prepared bases (except the tetrahydro bases such as *VI*) are given in Table I, their UV spectra in Table II. Positive Cotton effects (CE) above 300 nm (322 – 324 nm and 310 – 312 nm) and a negative one at 283 – 284 nm due to the sharp electronic transition at 284 nm (Table II), correspond to configuration (*R*) in the 4,4-disubstituted bases *VII* and *VIII* and to configuration (*S*) in the 5,5-disubstituted bases *XVII* and *XVIII*. CD spectra of position isomeric bases of opposite absolute configuration have thus the same course. This is connected with the fact (as seen *e.g.* from comparison of (*R*)-(+)-*VII* and (*S*)-(−)-*XVII*) that orientation of the substituents at the asymmetric center relative to the acylpyrido[3,4-*b*]indole chromophore plane is the same. However, the small number of compounds studied does not allow an interpretation of this fact (postulation of a sector rule).

In canthine-4,6-diones *XIX* and *XX* the CD measurements revealed an electronic transition at 255 – 259 nm, not detectable in the UV spectra. The longest-wave UV transition at 350 nm corresponds exactly to zero-value in the CD spectrum. Instead of the expected CE, the spectrum exhibits a pair of CD bands of opposite sign at 362 to 366 and 322 nm, the existence of which can be ascribed to several factors[4]. The CE at the longer wavelength is positive if the configuration at $C_{(5)}$ is (*R*).

EXPERIMENTAL

Boiling and melting points (Boetius block) are uncorrected. Analytical samples were dried at room temperature and 1,4 Pa for 6 h. The purity of the compounds was checked by thin-layer chromatography on commercial silica gel GF_{254} plates (Merck, FRG) in appropriate solvent systems or by gas–liquid chromatography on a Chrom III IKZ instrument (Labora, Czechoslovakia). Preparative thin-layer chromatography was carried out on 0·1 × 20 × 20 cm plates of silica gel GF_{254} in benzene–chloroform–methanol (90 : 45 : 10). UV spectra were determined on a Specord UV-VIS spectrophotometer, IR spectra on a UR 10 spectrophotometer (both Zeiss, GDR) ^{1}H NMR spectra were taken on a BS 487 instrument (Tesla, Czechoslovakia) and mass spectra on MS 902 spectrometer (AEI, England). Optical rotations were measured on a Zeiss Opton (FRG) polarimeter at 578 nm and 22 – 23°C. CD spectra were determined on JASCO UV/ORD/CD-5 (Japan Spectroscopic Company, Japan) and Roussel–Jouan II (Jouan, France) instruments.

* As shown by preliminary measurements, performed on a JASCO UV/ORD/CD-5 spectropolarimeter, this instrument is not suitable for measurements on bases of this type. Thus, both enantiomers of VIII afforded identical CD spectra; the only two marked, sharp, CD bands of opposite sign, $\Delta\varepsilon = -2{\cdot}05$ (287 nm) and $\Delta\varepsilon = +2{\cdot}1$ (283 nm), related to the electronic transition at 284 nm, are obviously artefacts.

(*R*)-(+)-2-Ethyl-2-methyl-3-methoxycarbonylpropionic Acid (*III*)

Dehydroabietylamine (24·0 g; 84·0 mmol) and the ester-acid[1,3] *III* (14·0 g; 84·0 mmol) were mixed in hot methanol (100 ml) and after concentration to about 75 ml the mixture was allowed to crystallize. The separated crystals (19·4 g; m.p. 131–140°C) were crystallized three times from methanol, affording 8·4 g (44%) of the salt, m.p. 144–147°C, $[\alpha]_D$ +27·0° (*c* 1·07; methanol). For $C_{28}H_{45}NO_4$ (459·6) calculated: 73·16% C, 9·87% H, 3·05% N; found: 73·17% C, 9·94% H, 3·14% N. The salt (7·5 g) was partitioned between saturated sodium hydrogen carbonate solution (90 ml) and dichloromethane (100 + 75 ml). The aqueous phase was diluted with water (40 ml), acidified with 5% hydrochloric acid (pH 2) and extracted with dichloromethane (60 + 40 ml). The combined extracts were washed with water (30 ml), dried over anhydrous sodium sulfate, and taken down *in vacuo*, leaving a thick oil, [α] +8·6° (*c* 3·83; methanol). Although the product was homogeneous according to gas-liquid chromatography, it resisted to crystallization attempts,

TABLE I

CD Spectra of 4,4- and 5,5-disubstituted canthinones (in methanol at 22–24°C)

Base	Δε, nm			
(*R*)-(+)-*VII*[a]	+1·40 (322),	+1·25 (312),	0·0 (295),	−0·65 (284)
(*R*)-(+)-*VIII*	+1·75 (322),	+1·15 (310),	0·0 (297),	−0·75 (284)
(*S*)-(−)-*XVII*	+1·05 (324),	+0·80 (311),	0·0 (295),	−0·80 (283)
(*R*)-(+)-*XVIII*	−0·90 (324),	−0·65 (311),	0·0 (296),	+0·95 (284)
(*S*)-(−)-*XIX*	−2·40 (366),	0·0 (350),	+1·75 (332),	+0·60 (303),
	0·0 (290),	−1·95 (274)		
(*R*)-(+)-*XX*	+1·10 (362),	0·0 (351),	−1·35 (332),	−0·50 (304),
	0·0 (290),	+1·35 (273),	+1·15 (255)	

[a] Optical purity 83%.

TABLE II

UV Spectra of canthinones (in methanol)

Base	λ_{max}, nm (log ε)			
VII, VIII, XVII, XVIII	329 (3·87),	317 (3·82),	284 (4·16)	
	274 (4·08),	265 (4·14),	230 sh (4·52)	
XIX, XX	351 (3·60),	307 (3·88),	269 (3·99)	
	231 (4·43)			
VI	334 sh (3·91),	317 (4·11),	230 (4·16)	

(*R*)-(+)-Dimethyl 2-Ethyl-2-methylbutanedioate (*IV*)

An ethereal solution of diazomethane was added dropwise to a solution of the acid (*R*)-(+)-*III* (0·480 g; 2·76 mmol) in ether (7 ml) till the yellow colouration persisted. After standing overnight the solution was taken down and the residue was distilled *in vacuo*, affording 0·460 g (89%) of a liquid, b.p. 85–86°C/1·14 kPa; purity 98% (gas–liquid chromatography); $[\alpha]$ +7·5° (neat). Reported[2] $[\alpha]$ −8·95° (neat) for the enantiomeric compound.

(*R*)-(+)-N-[2-(Indol-3-yl)ethyl]-2-ethyl-2-methyl-3-methoxycarbonylpropanamide (*V*)

The acid (*R*)-(+)-*III* (1·40 g; 8·04 mmol) was converted by the described[1] procedure into material which was crystallized twice from a mixture of chloroform, absolute ether and hexane, affording 1·38 g (54%) of crystals, m.p. 101·8–103·4°C, $[\alpha]$ +18·9° (*c* 2·90; ethanol). For $C_{18}H_{24}N_2O_3$ (316·4) calculated: 68·33% C, 7·65% H, 8·85% N; found: 68·30% C, 7·70% H, 8·96% N.

(*R*)-(+)-4-Ethyl-4-methyl-1,2,3,4-tetrahydro-6*H*-canthin-6-one (*VI*)

Tryptamide (*R*)-(+)-*V* (0·400 g; 1·26 mmol) was converted by the described procedure[1] into 0·150 g (46%) of a glass, uniform according to thin-layer chromatography; $[\alpha]$ +29·9° (*c* 2·17; chloroform). IR, ^{1}H NMR and mass spectra of the product were identical with those of the racemate[1].

(*R*)-(+)-4-Ethyl-4-methyl-4,5-dihydro-6*H*-canthin-6-one (*VII*)

The base (*R*)-(+)-*VI* (0·050 g; 0·19 mmol) was transformed[1] into a thick oil (0·040 g; 79%), $[\alpha]$ +16·6° (*c* 2·29; chloroform). Picrate m.p. 202–205°C (ethanol). For $C_{23}H_{19}N_5O_8$ (493·4) calculated: 55·98% C, 3·88% H, 14·19% N; found: 56·04% C, 3·93% H, 14·29% N.

(*R*)-(+)-Dimethyl 2-Ethyl-2-propylbutanedioate (*X*)

The diester (*R*)-(−)-*XI* was hydrogenated[1] to give 84% of an oil of 97% purity (according to gas–liquid chromatography); $[\alpha]$ +2·23° (neat). Its ^{1}H NMR, IR and mass spectra were identical with those of the racemate[1].

(*S*)-(−)-3-Methyl-3-methoxycarbonylpentanoic Acid (*XII*)

Alkaline hydrolysis[1] of the ester (*S*)-(−)-*IX* (1·64 g; 8·71 mmol) afforded 1·35 g (89%) of a viscous liquid, $[\alpha]$ −10·8° (*c* 5·28; methanol); purity 97% (gas–liquid chromatography). For the enantiomer of 78% optical purity reported[5] $[\alpha]_D$ +8·5; ethanol). Except the rotation, the product was identical with the racemic acid[1].

(*R*)-(+)-3-Ethyl-3-methoxycarbonylhexanoic Acid (*XIII*)

The title compound was prepared from the dimethyl ester (*R*)-(+)-*X* according to ref.[1] in 95% yield. The obtained thick oil was 98% pure (gas–liquid chromatography); $[\alpha]$ +0·7 ± 0·9° (*c* 5·65; methanol), its IR and ^{1}H NMR spectra were identical with those of the racemate[1].

(*S*)-(−)-N-[2-(Indol-3-yl)ethyl]-3-methyl-3-methoxycarbonylpentanamide (*XV*)

Prepared from the acid (*S*)-(−)-*XII* in 62% yield by the described procedure[1]. The glassy homogeneous (thin-layer chromatography) product had [α] −2·1° (*c* 4·86; ethanol); its spectral (IR, mass) properties corresponded to those of the racemic compound[1].

(*R*)-(+)-N-[2-(Indol-3-yl)ethyl]-3-ethyl-3-methoxycarbonylhexanamide (*XVI*)

The title compound was prepared in 65% yield from the ester-acid (*R*)-(+)-*XIII* using the described[1] procedure. M.p. 88·5–91·5° (chloroform–ether–light petroleum); [α] +1·3° (*c* 4·80; ethanol). For $C_{20}H_{28}N_2O_3$ (344·4) calculated: 69·74% C, 8·19% H, 8·13% N; found: 69·47% C, 8·25% H, 8·10 N.

(*S*)-(−)-5-Ethyl-5-methyl-4,5-dihydro-6*H*-canthin-6-one (*XVII*)

The base was obtained in 32% yield from (*S*)-(−)-*XV* as described in ref.[1]. It melted at 82·5 to 84·5°C; [α] −1·8° (*c* 2·22; chloroform); its IR, ^{1}H NMR and mass spectra were identical with those of the racemic base[1].

(*R*)-(+)-5-Ethyl-5-propyl-4,5-dihydro-6*H*-canthin-6-one (*XVIII*)

Obtained by the described procedure[1] in 36% yield from the tryptamide (*R*)-(+)-*XVI* as a glass; [α] +0·8° (*c* 2·15; chloroform). Picrate m.p. 194–195·5°C (ethanol). For $C_{25}H_{23}N_5O_8$ (521·5) calculated: 57·58% C, 4·45% H, 13·43% N; found: 57·45% C, 4·56% H, 13·49% N.

(*S*)-(−)-5-Ethyl-5-methyl-4,5-dihydro-6*H*-canthin-4,6-dione (*XIX*)

Prepared[1] in 30% yield from tryptamide (*S*)-(−)-*XV* as a glass, [α] −16·7° (*c* 0·78; chloroform) which had IR, ^{1}H NMR and mass spectral properties identical with the racemic base[1].

(*R*)-(+)-5-Ethyl-5-propyl-4,5-dihydro-6*H*-canthin-4,6-dione (*XX*)

Prepared according to ref.[1] from tryptamide (*R*)-(+)-*XVI* in 35% yield; glass of [α] +12·2° (*c* 1·47; chloroform); its ^{1}N NMR, IR and mas spectra were identical with those of the racemic compound[1].

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