ABSOLUTE CONFIGURATION OF (R)-(—)-2-ALLYL-2-ETHYL-3-METHOXYCARBONYLPROPIONIC ACID*,**

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The absolute configuration of (*R*)-(−)-2-allyl-2-ethyl-3-methoxycarbonylpropionic acid (*I*) was determined on the basis of the conversion of *I* to dimethyl (*S*)-(−)-2-ethyl-2-methylsuccinate (*X*) and (*R*)-(+)-4-ethyl-4-propyl-4,5-dihydro-6*H*-canthin-6-one (*XIV*).

In the preceding paper[1] we have described the total synthesis of racemic 4,4- and 5,5-disubstituted canthin-6-ones. For the preparation of these bases with a defined absolute configuration it was indispensable to determine the absolute configuration of its key intermediate – 2-allyl-2-ethyl-3-methoxycarbonylpropionic acid (*I*).

The starting substance for the synthesis of optically active acid *I* was 2-cyano-2-ethyl-4-pentenoic acid[2] (*II*) which was resolved by five-fold crystallization of its salt with (+)-L-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol from aqueous methanol. From the salt obtained we set (+)-acid *II* free which was then converted in the known manner[2] by Arndt–Eistert reaction *via* acyl chloride (−)-*III* and diazoketone (+)-*IV* to the corresponding esters of 3-cyano-3-ethyl-5-hexenoic acid (−)-*V* and (−)-*VI*. Both cyano esters were submitted to alkaline hydrolysis and subsequent reaction with acetyl chloride affording[2] (−)-2-allyl-2-ethylsuccinic anhydride (*VII*). It is known that the use of various catalysts affects the optical purity of the products of Wolff's rearrangement[3]. In this connection it deserves mention that the cyano esters (−)-*V* and (−)-*VI* afforded succinic anhydride (−)-*VII* of the same specific rotation $[\alpha]$ −24·6° (chloroform), corresponding to 100% optical purity.

Finally, on treatment of anhydride (−)-*VII* with methanol we prepared an oily (−)-2-allyl-2-ethyl-3-methoxycarbonylpropionic acid (*I*) of specific rotation $[\alpha]$ −9·8° (methanol). Absolute configuration (*R*) of this acid was determined on the basis of chemical correlation in two independent ways:

The ester-acid (−)-*I* was treated with diazomethane affording dimethyl (*R*)-(−)-2-allyl-2-ethylsuccinate (*VIII*) from which we prepared aldehyde-ester (−)-*IX* using the method of Lemieux–Johnson[4]. Then we degraded the formylmethyl group

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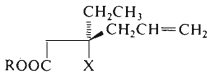
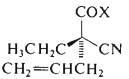
in (−)-*IX* to the methyl group using[5] rhodium-tris(triphenylphosphine) chloride. In this manner we obtained dimethyl (*S*)-(−)-2-ethyl-2-methylsuccinate[6] (*X*) with specific rotation [α] −8·95° (subst.). From this the absolute configuration of the acid (*R*)-(−)-*I* follows, as well as its 100% optical purity (according to ref.[6] the value for (*S*)-(−)-*X* was [α] −8·87° (subst.)).

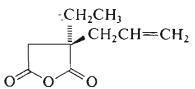
On hydrogenation of ester-acid (*R*)-(−)-*I* on Adams catalyst we obtained (+)-2--ethyl-3-methoxycarbonyl-2-propylpropionic acid (*XI*) the transformation of which



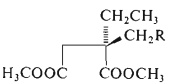


(−)-(*R*)-*I*, X=COOH, R=CH_3
(−)-(*R*)-*V*, X=CN, R=CH_2CH_3
(−)-(*R*)-*VI*, X=CN, R=CH_3

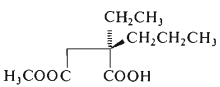
(+)-(*S*)-*II*, X= OH
(−)-(*S*)-*III*, X= Cl
(+)-(*S*)-*IV*, X= CH=N_2



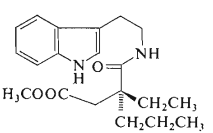
(−)-(*R*)-*VII*



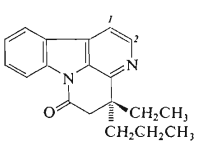
(−)-(*R*)-*VIII*, R= CH=CH_2
(−)-(*R*)-*IX*, R= CH=O
(−)-(*S*)-*X*, R= H



(+)-(*R*)-*XI*



(+)-(*R*)-*XII*



(+)-(*R*)-*XIII*, 1,2-dihydro
(+)-(*R*)-*XIV*

according to ref.[1] led to the degradation product of (+)-eburnamonine[7] – (+)-4--ethyl-4-propyl-4,5-dihydro-6*H*-canthin-6-one (*XIV*) with [α] +31·2° or +31·8° – *via* amide (+)-*XII* and base (+)-*XIII*. A comparison of this product with its enantiomer (*S*)-(−)-*XIV* ([α] −31·1° or −31·3°; *c* 2·9 or 0·5, respectively, in chloroform) obtained[1] on degradation of (+)-(16*S*,20*S*,21*S*)-vincamine[8] confirms the above determined absolute configuration of the acid (*R*)-(−)-*I*.

In view of simultaneously performed correlation to ester (*S*)-(−)-*X* the correlation of acid (*R*)-(−)-*I* with canthinone (*S*)-(−)-*XIV* also represents the first direct determination of the absolute configuration of eburnane alkaloids by chemical routes.

EXPERIMENTAL

The boiling and the melting points are not corrected (measured on a Boetius microblock). Analytical samples were dried at room temperature and 1·4 Pa pressure for 6 h. The purity of the substances was checked by thin-layer chromatography on commercial silica gel GF_{254} (Merck, GFR) or by gas chromatography on a CHROM III IKZ instrument (Labora, ČSSR). Preparative thin-layer chromatographies were carried out on 20 × 20 cm plates with a silica GF_{254} gel layer 1 mm thick, using benzene–chloroform–methanol 90 : 45 : 10 for development. The ultraviolet spectra were measured in methanol on a SPECORD UVVIS (Zeiss, Jena, GDR) spectrometer. The infrared spectra were recorded on a UR 10 (Zeiss, Jena, GDR) spectrophotometer. The ^{1}H NMR spectra were measured on a BS 487 (Tesla, CSSR) instrument; chemical shifts are given in δ-scale (ppm), using tetramethylsilane as internal reference. The mass spectra were measured on a high-resolution mass spectrometer with double-focusing, MS 902 (AEI, Great Britain), at 70 eV of ionizing electron energy. Specific rotations were measured on a subjective polarimeter Zeiss Opton (GDR) at 578 nm wavelength and 22 to 23°C.

(*S*)-(+)-2-*Cyano*-2-*ethyl*-4-*pentenoic acid* (II): (±)-2-Ethyl-2-cyano-4-pentenoic acid[2] (*II*) (115·0 g, 0·751 mol) and L-(+)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol (143·5 g, 0·676 mol [α] +30·5° (*c* 2·4; 1M-HCl)) were dissolved in hot water and the solution was allowed to crystallize freely, finally in a refrigerator. The precipitated salt (155·9 g, 113·5%) of m.p. 132·5 to 137·2°C was recrystallized five times from 15% aqueous methanol. After the fifth crystallization the yield was 53·6% (73·6 g) of the salt, melting at 124–125·5°C and with [α] +31·3° (*c* 4·0; ethanol). The salt (69 g, 188 mol) was distributed between 10% hydrochloric acid (150 ml) and ether (250 ml) and the aqueous phase was extracted with ether (100 and 2 × 50 ml). The combined ethereal extracts were washed with 3% hydrochloric acid (50 ml), water (50 ml) and brine (60 ml). After drying over anhydrous sodium sulfate and filtration the extract was evaporated affording 27·8 g (48·3%) of an oil with [α] +5·4° (*c* 7·4, acetic acid), identical according to its ^{1}H NMR spectrum[2] with the racemic acid *II*.

(S)-(−)-2-*Cyano*-2-*ethyl*-4-*pentenoyl chloride* (III): According to ref.[2] acid (*S*)-(+)-*II* (27·8 g; 181·5 mmol) afforded 25·6 g (82%) of a liquid boiling at 90–90·6°C/1·3 kPa; [α] −2·9° (*c* 5·2, chloroform); purity 97% according to GLC.

(S)-(+)-3-*Cyano*-1-*diazo*-3-*ethyl*-5-*hexen*-2-*one* (IV): According to ref.[2] chloride (*S*)-(−)-*III* (24·9 g; 145·0 mmol) gave 27·0 g (105%) of crude diazo ketone, as a yellow oil, [α] +45·6° (*c* 7·2, chloroform); purity 88% according to GLC.

Ethyl (R)-(−)-3-*cyano*-3-*ethyl*-5-*hexenoate* (V): From crude diazoketone (*S*)-(+)-*IV* (20 g; corresponding to 107 mmol) an oil was obtained according to ref.[2], weighing 14·3 g (68%) and boiling at 132—135°C/1·54 kPa, with $[\alpha]$ −9·4° (*c* 6·1, ethanol); purity 97% according to GLC.

Methyl (R)-(−)-3-*cyano*-3-*ethyl*-5-*hexenoate* (VI): Crude diazoketone (*S*)-(+)-*IV* (6·8 g; corresponding to 36 mmol) gave according to ref.[2] 4·4 g (66%) of an oil with $[\tau]$ −10·1° (*c* 5·0, methanol); purity 97% according to GLC.

(R)-(−)-2-*Allyl*-2-*ethylsuccinic anhydride* (VII): When working according to ref.[2] cyanoester (*R*)-(−)-*V* (19·0 g; 97·5 mmol) gave 14·2 g (87%) of an oil with b.p. 134—135°C/1·72 kPa and $[\alpha]$ −24·6° (*c* 6·3, chloroform); purity 98% according to GLC. On hydrolysis of ester (*R*)-(−)-*VI* and reaction with acetyl chloride the same anhydride was obtained, also having the same specific rotation.

(R)-(−)-2-*Allyl*-2-*ethyl*-3-*methoxycarbonylpropionic acid* (I): This was prepared according to ref.[1] from 13·65 g (81 mmol) of succinic anhydride (*R*)-(−)-*VII* in a 91% yield (14·85 g), $[\alpha]$ −9·76° (*c* 8·2, methanol); purity 90% according to GLC.

Dimethyl (R)-(−)-2-*allyl*-2-*ethylsuccinate* (VIII): Operating as in ref[1]. 8·62 g (43 mmol) of acid (*R*)-(−)-*I* gave 8·67 g (94%) of a liquid with b.p. 116·5—117·7°C/1·4 kPa and $[\alpha]$ −9·53° (subst.); purity 96% according to GLC.

(±)-*Dimethyl* 2-*ethyl*-2-(*formylmethyl*)*succinate* (IX): Osmium tetroxide (0·50 g; 2·0 mmol) was added to a solution of 6 g (28 mmol) of racemic diester[1] *VIII* in 160 ml of tetrahydrofuran and 165 ml of water and the mixture was stirred at room temperature and under nitrogen for 40 min. Sodium periodate (14·7 g; 69 mmol) was then added in small portions over 45 min and the mixture was stirred at room temperature for 52 h, when the reaction was terminated (according to TLC analysis). After filtration and evaporation of tetrahydrofuran the concentrated mixture was extracted with benzene (200 ml and 3 × 75 ml). The combined benzene phases were washed with two 50 ml portions of water, 5% potassium pyrosulfate solution (2 × 70 ml), again with water (2 × 50 ml) and finally with brine (60 ml). After drying the extract was evaporated and the residue filtered through a silica gel column (30 g; benzene and benzene–chloroform 10 : 1 were used for elution). The eluate was evaporated and the residue distilled under reduced pressure. The fraction boiling at 60—63°C/6 Pa was collected (4·04 g; 66·75%) and its purity was 99% according to GLC. IR spectrum in CCl_4: 2 890 (OCH_3), 2 850 and 2 740 (CHO), 1 740 (ester), 1 721 cm^{-1} (aldehyde). ^1H NMR spectrum in $CDCl_3$: 9·80 (1 H, t, J = 1·5 Hz; C—CH_2—CH=O); 3·75 and 3·67 (2 × 3 H, s; $COOCH_3$); 2·97 (2 H, d, J = 1·5 Hz; C—CH_2—CH=O); 2·92 and 2·70 (2 × 1 H, d, ABq, J = 16·5 Hz; C—CH_2—CO—); 1·75 (2 H, m; CH_3—CH_2—C); 0·87 (3 H, t, J = 7·0 Hz; CH_3—CH_2—C). Mass spectrum: m/z 216 (M^+, $C_{10}H_{16}O_5$).

Dimethyl (R)-(−)-2-*ethyl*-2-(*formylmethyl*)*succinate* (IX): this was prepared analogously from dimethyl ester (*R*)-(−)-*VIII* (6·40 g; 30 mmol) in a 68% yield (4·38 g) in the form of an oil with b.p. 64—66°C/8 Pa and $[\alpha]$ −8·15° (*c* 3·7; chloroform); purity 99% according to GLC.

Dimethyl (±)-2-*ethyl*-2-*methylsuccinate* (X): A mixture of 3·40 g (15·7 mmol) of aldehyde-ester (±)-*IX*, 15·7 g (17·0 mmol) of rhodium-tris (triphenyl-phosphine) chloride[9] and acetonitrile (300 ml) was refluxed for 12 h. According to GLC the reaction was over, and the yellow rhodium-bis(triphenylphosphine)carbonyl chloride (10·5 g; 89%) filtered off. After concentration in a vacuum the residue was triturated with 2 portions of hexane (20 ml). The combined organic phases were evaporated and 30 ml of hexane were added to the residue. The solution was cooled, filtered and evaporated. The residue was distilled in a vacuum to give 1·43 g (48%) of an oil with b.p. 89·5—90·0°C/1·2 kPa of 98% purity according to GLC.

Dimethyl (S)-(−)-2-*ethyl*-2-*methylsuccinate* (X): In an analogous experiment 4·11 g (19·0 mmol) of aldehyde-diester (*R*)-(−)-*IX* gave 1·72 g (48%) of a liquid boiling at 89·9−90·5°C/1·2 kPa and having [α] −8·95° (substance); purity 98% according to GLC.

(*R*)-(+)-2-*Ethyl*-3-*methoxycarbonyl*-2-*propylpropionic acid* (XI): This was obtained according to ref.[1] by catalytic hydrogenation of acid (*R*)-(−)-*I* (5·59 g; 27·8 mmol) in a 93·5% yield (5·28 g), as an oil with [α] +3·5° (*c* 8·0; methanol) and 89% purity according to GLC.

(R)-(+)-N-[2-(*Indol*-3-*yl*)*ethyl*]-2-*ethyl*-3-*methoxycarbonyl*-2-*propylpropanamide* (XII): This was prepared from acid (*R*)-(+)-*XI* (2·6 g; 12·8 mmol) according to ref.[1] in a 56% yield (2·49 g); m.p. 86−88°C, [α] +3·65° (*c* 4·1; ethanol), homogenous according to TLC.

(R)-(+)-4-*Ethyl*-4-*propyl*-1,2,4,5-*tetrahydro*-6H-*canthin*-6-*one* (XIII): This was prepared from tryptamide (*R*)-(+)-*XII* according to ref.[1] in a 37% yield of a glassy substance, homogeneous according to TLC, [α] +5·0° (*c* 2·0; chloroform).

(R)-(+)-4-*Ethyl*-4-*propyl*-4,5-*dihydro*-6H-*canthin*-6-*one* (XIV): Dehydrogenation with selenium of (*R*)-(+)-tetrahydro-6*H*-canthin-6-one (*XIII*) according to ref.[1] gave 77% of glass, homogeneous according to TLC, with [α] +31·2° (*c* 1·9; chloroform). Its picrate was prepared in the conventional manner, m. p. 188−190°C (ethanol).

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