PREPARATION OF OPTICALLY ACTIVE 3-CYCLOPENTYL-3-METHYL-2-AZETIDINONE

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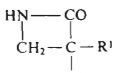
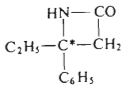
The resolution of 2-cyclopentyl-2-cyanopropanoic acid gave its enantiomers, which by esterification and hydrogenation were transformed into (+) and (−)-methyl-(3-amino-2-cyclopentyl-2-methyl)propanoate. Their cyclization yielded both enantiomers of 3-cyclopentyl-3-methyl-2-azetidinone.

3,3-Disubstituted 2-azetidinones (α,α-disubstituted β-lactams, I) are the only lactams that can be polymerized anionically without side reactions[1]. By using these lactams, the first "living" anionic polymers of lactams could be prepared[2], thus opening a route for the synthesis of structurally homogeneous polyamides and copolyamides. A question arose in this connection, whether under suitable conditions the polymer of the optically active α,α-disubstituted β-lactam may form preferred conformations, *e.g.*, helix. A similar study has already been carried out with polymers of the β-substituted and α,β-disubstituted β-lactam[3] and with a polycondensate of the β-substituted β-amino acid[4]; the results were negative. With respect to the disturbing influence of side reactions, however, these polymers may have contained foreign structural units which change the direction of the order of monomer units[1], thus impeding the formation of secondary structures.

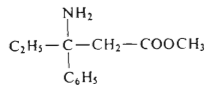
So far, neither the simple optically active α,α-disubstituted four-membered lactam of type *I* nor its suitable precursor have been described. Resolution of the racemic lactam by crystallization from the melt, successful with the α-substituted and α,β-disubstituted lactam[5], cannot be considered in our case, because the lactam is a liquid



I



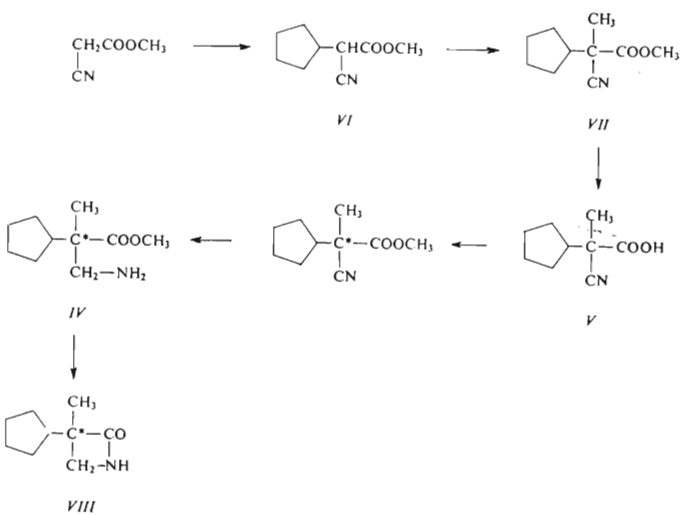
II



III

one. Synthesis of the optically active β,β-disubstituted lactam *II* was performed with β,β-disubstituted aminopropanoate *III*, which was resolved using (−)-dibenzoyltartaric acid[6]. Attempts at performing a similar resolution of the precursor of lactam *I*, *e.g.* methyl-β-amino-α-cyclopentyl-α-methylpropanoate ((±)-*IV*) by using (−)-dibenzoyltartaric acid have failed.

A better hope for resolution could be expected for α,α-disubstituted β-aminopropanoic acid with a protected amino group, or α,α-disubstituted cyancacetic acid (*V*). Resolution of acid *V* by means of quinine gave both enantiomers, from which amino esters were obtained by esterification followed by hydrogenation. These were cyclized to lactams by means of the Grignard reagent (Scheme 1).



SCHEME 1

After the lactams were purified by column chromatography and distillation, optical purity of (−)-lactam was 1·00, that of (+)-lactam was 0·83 (Table I). Optical purity of the intermediates was not determined.

EXPERIMENTAL

(±)-Methyl-2-cyclopentyl Cyano Acetate (*VI*)

Similarly to butylation[7], 388 g (3·96 mol) of methyl cyanoacetate was alkylated with cyclopentyl bromide, which after rectification gave 190 g (28%) of *VI*, b.p. 123°C/1·3 kPa, GLC purity 97·8–98·6%. The ^{1}H NMR spectrum (ppm): 1·60 (m, 8 H, ring CH_2), 2·40 (m, 1 H, —CH ring), 3·34 (d, J = 6·2 Hz, 1 H, CH—CN), 3·78 (s, 3 H, CH_3—O). For $C_9H_{13}NO_2$ (167·2), calculated: 64·65% C, 7·84% H, 8·38% N; found: 63·89% C, 7·96% H, 8·25% N.

(±)-Methyl-2-cyclopentyl-2-cyanopropanoate (*VII*)

Methylation of 161 g (0·96 mol) of *VI* by employing a procedure already described[7] gave 121·4 g (70%) of *VII*, b.p. 126–127°C/1·8 kPa, GLC purity 99·7%. ^{1}H NMR spectrum (ppm): 1·52 (s, 3 H, 2-methyl), 1·56 (m, 8 H, circular CH_2), 2·22 (m, 1 H, 1-CH ring), 3·72 (s, 3 H, CH_3—O—). For $C_{10}H_{15}NO_2$ (181·2), calculated: 66·27% C, 8·34% H, 7·72% N; found: 65·48% C, 8·36% H, 7·61% N.

(±)-2-Cyclopentyl-2-cyanopropanoic Acid (*V*)

Hydrolysis of 63·2 g of *VII* in a water–ethanol solution of potassium hydroxide gave after workup 56·6 g (97%) of raw acid, b.p. 147°C/0·24 kPa, after triple crystallization 34·5 g, m.p. 56·5 to 58·5°C (ligroin–diethyl ether). IR (2·2% in CCl_4): 1 715, 2 250, 2 870, 2 960 and diffusion 2 700 to 3 400 cm^{-1}. For $C_9H_{13}NO_2$ (167·2) calculated: 64·65% C, 7·84% H, 8·38% N; found: 64·55% C, 7·96% H, 8·44% N.

TABLE I

Characteristics of sol fractions *V* after resolution, of intermediate products *VII* and resulting lactams *VIII*

Characteristics	L_5	D_7
	V	
Weight, g	14·8	31·7
$[\alpha]_0$ ($CHCl_3$)	−123·7 (*c* 3·3)	−107·0 (*c* 4·5)
	VII	
Weight, g	3·74	10·1
$[\alpha]_0$ (toluene)	−19·1 (*c* 3·2)	+14·0 (*c* 4·6)
	VIII	
Weight, g	1·87	4·16
$[\alpha]_D$ (toluene)	−22·7 (*c* 4·8)	+16·8 (*c* 4·2)
$[\Theta]_{186}$[a]	−9·35	+3·51
$[\Theta]_{213}$[a]	+2·13	−1·93
Enantiomeric purity[b]	1·00	0·83

[a] Molar ellipticity at 186 and 213 nm, (deg. cm^2 dmol^{-1}) . 10^{-3}, [b] according to ^{1}H NMR.

RESOLUTION

The salt was prepared by mixing a solution of 47·6 g (284 mmol) of acid *V* with a suspension of 92·3 g (284 mmol) of quinine in a total volume of 2·3 l of acetone, refluxing the mixture for 1 h and filtration after 16 h at 10°C. Yield 63·3 g of the salt, m.p. 189–191°C (decomp.), $[\alpha]_D$ −114·8° (*c* 3·8, $CHCl_3$). For $C_{29}H_{37}N_3O_4$ (491·6), calculated: 70·85% C, 7·59% N; found: 70·89% C, 7·66% H, 8·48% N.

By crystallizing the salt in a ratio 15 g of salt per 1 l of acetone, five fractions were successively obtained (L_1–L_5, weights 49·7, 34·2, 27·1, 19·3 and 14·8 g); fraction L_5 had $[\alpha]_D$ −123·7° (*c* 3·3, $CHCl_3$). Concentration of mother liquors to half the initial volume repeated five times and followed by filtration with sucking of the sedimented fractions gave five fractions (D_1–D_5, weights 10·5, 30·7, 8·6, 7·7 and 8·4 g). The last mother liquors were evaporated, and after the addition of 150 ml of diethyl ether 8·8 g of fraction D_6 was obtained, $[\alpha]_D$ −110° (*c* 4·2, $CHCl_3$). Combined crystallization of intermediate fractions and mother liquors gave moreover 15·5 g of fraction L_6, $[\alpha]_D$ −121·4° (*c* 3·6, $CHCl_3$), 11·6 g of fraction L_7, $[\alpha]_D$ −119° (*c* 4·2, $CHCl_3$) and 31·7 g of fraction D_7, $[\alpha]_D$ −107° (*c* 4·5, $CHCl_3$).

3-Cyclopentyl-3-methyl-2-azetidinone (*VIII*)

Acid *V* released from fractions L_5 and D_7 was reesterified with diazomethane, the cyano esters *VII* thus obtained were hydrogenated to aminopropanoate *IV*, which were cyclized after repurification; all these operations were carried out under described conditions[7] with similar yields. The optically active lactams *VIII* eventually obtained were purified by distillation, column chromatography (SiO_2, 7% H_2O, elution with benzene–chloroform), and redistillation. The yields and characterization of the purest fractions are given in Table I. For $C_9H_{15}NO$ (153·2), calculated: 70·55% C, 9·87% H, 9·14% N; found: 70·47% C, 9·89% H, 9·05% N. ^{1}H NMR spectrum (ppm): 1·24 (s, 3 H, methyl), 1·61 (m, 9 H, cyclopentyl), 2·99 (q, J = 5·5 Hz —CH_2— lactam), 7·25 (s, 1 H, NH).

Analytical Methods

Purity of the compounds was determined by gas chromatography using a Perkin–Elmer F 11 apparatus (column 2 m, 15% Ge-XE 60 on Chromosorb W). The infrared spectra were recorded with a Perkin–Elmer 457 apparatus, the ^{1}H NMR spectra were measured with a JEOL-PS 100 apparatus in CCl_4. Chemical shifts are referred to hexamethyldisiloxane as the internal standard (0·05 ppm). Specific rotations were determined at room temperature with an Opton photoelectric precision polarimeter 0·005°; the CD-spectra of lactams in 2,2,2-trifluoroethanol were recorded with a Cary 61 spectropolarimeter (0·02 mol l^{-1}). Optical purity of the lactams was determined by ^{1}H NMR spectrometry. 0·5 mol l^{-1} solutions of the lactam and 0·3 mol l^{-1} solutions of the shift reagent in tetrachloromethane were prepared, allowing the NH proton signals in the individual enantiomers to be resolved by 0·26 ppm; the relative content was determined by integration of these peaks. Tris-(3-trifluoroacetyl-(+)-camphorato)-Eu(III) was used as the shift reagent

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REFERENCES

1. Šebenda J. in the book: *Structural Order of Polymers* (F. Ciardelli, P. Giusti, Eds), p. 95. Pergamon Press, Oxford 1981.
2. Šebenda J., Hauer J.: Polymer Bull. *5*, 529 (1981).
3. Schmidt E.: Angew. Makromol. Chem. *14*, 185 (1970).
4. Abbott R. F.: *Thesis*. Polytechnic Institute of Brooklyn, New York 1967.
5. Jensen H.: Ger. Offen. 1 807 495 (11. 6. 1970).
6. Fontanella L., Testa E.: Justus Liebigs Ann. Chem. *616*, 148 (1958).
7. Šebenda J., Hauer J., Biroš J.: J. Polym. Sci., Polym. Chem. Ed. *14*, 2357 (1976).

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