SYNTHESIS OF 1-(α-PHENYLETHYL)AZETIDIN-2-ONES

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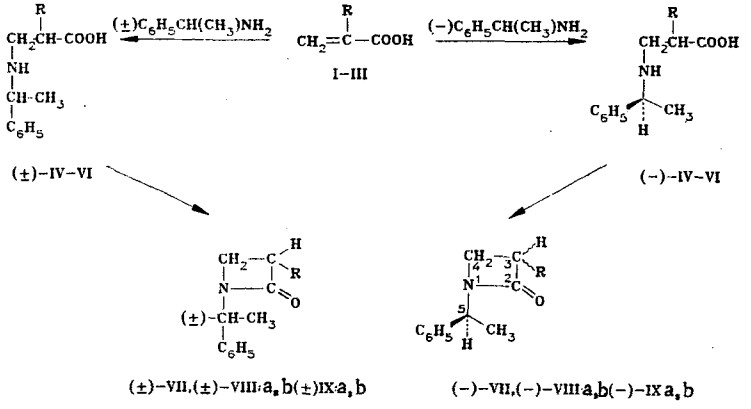
Phase-transfer catalyzed cyclization of racemic and optically active N-substituted β-aminoacids has given racemic and optically active 2-azetidinones, the spatial structures of which have been established by NMR spectroscopy. The original β-aminoacids were obtained by adding α-phenylethylamine to substituted acrylic acids.

In a study of asymmetric syntheses and the reactivity of 2-azetidinones, some of which possess a wide spectrum of biological activity [1, 2], we here report the preparation of N-(α-phenylethyl)-β-aminoacids (IV-VI) by the addition [1, 3, 4] of racemic or (—)-α-phenylethylamine to α-substituted acrylic acids (I-III). The IR spectra of the β-aminoacids display typical absorption at 1580 (COO^-) and 2280-2200 cm^{-1} ($\overset{+}{N}H_2$), indicating that they possess the betaine structure. The β-aminoacids obtained (in 40-60% yields) were used without further purification for the synthesis of the 2-azetidinones.

Japanese workers [5] have recently shown that it is possible in principle to close the azetidinone ring by a two-phase reaction. Using tetrabutylammonium hydrogen sulfate as the phase-transfer catalyst, the β-aminoacids obtained were cyclized to the 2-azetidinones (VII-IX).



I, IV, VII R=H; II, V, VIII R=CH_3; III, VI, IX R=C_6H_5

The occurrence in (VIII) and (IX) of two ($C_{(3)}$ and $C_{(5)}$) chiral centers should afford a diastereoisomeric pair on cyclization.

It was in fact found that the PMR spectra of both the optically active and racemic 2-azetidinones (VIII) showed a doubling of the signals for the 3-CH_3 group and the methine proton of the α-phenylethyl substituent. The ratios of the intensities of these signals demonstrate the formation of the diastereoisomers in a ratio of 1:1. The ^{13}C NMR spectra also showed doubling of the signals for $C_{(3)}$, $C_{(5)}$, and the 3-CH_3 group.

However, chromatography of the reaction products on different sorbents (silica and alumina) and in systems of differing polarity did not reveal the presence of two isomers. A more careful choice of the conditions for chromatographic analysis on Silufol (previously impregnated with methanol, followed by elution with the system benzene—ethyl acetate, 2:1, and twice with ether) revealed the presence of two isomers of the azetidinone (VIII) with very similar chromatographic mobilities (R_f 0.37 and 0.32).

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TABLE 1. 2-Azetidinones

Compound *	R	R_f †	$[\alpha]_D^{20°}$ in CCl_4 (c, %)	νCO, cm^{-1}	Yield, %
(±)-VII	H	0,35	—	1760	30
(−)-VII	H	0,35	−37,8 (0,8)	1760	32
(±)-VIIIa	CH_3	0,37	—	1750	25
(±)-VIIIb	CH_3	0,32	—	1750	
(−)-VIIIa	CH_3	0,37	−19,9 (0,6)	1750	28
(−)-VIIIb	CH_3	0,32	−32,3 (1,0)	1750	
(±)-IXa	C_6H_5	0,71	—	1750	20
(±)-IXb	C_6H_5	0,62	—	1760	
(−)-IXa	C_6H_5	0,71	−25,6 (0,7)	1750	26
(−)-IXb	C_6H_5	0,62	−75,1 (0,8)	1760	

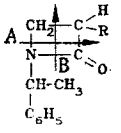
*Mp of (±)-(IXa), 82-84; (−)-(IXa), 68-69, (−)-(IXb), 49-50°C. The remaining compounds were obtained as oils.
†Silufol UV-254, benzene—ethyl acetate, 2:1.

The pure diastereoisomers of (VIII) were then separated. Using a specially developed method of separation by preparative chromatography on plates with methanol-impregnated Silperal UV-254, followed by threefold elution with benzene—ethyl acetate, 2:1 (up to half the height of the plate), then twice with ether (to the end of the plate), the pure diastereoisomeric 2-azetidinones were isolated, also in a weight ratio of 1:1.

Chromatographic analysis of the reaction mixture of (IX) also failed to reveal clearly the formation of a diastereoisomeric pair, but it proved possible by separation of the reaction mixture on a silica columm (L 40/100, benzene—ethyl acetate, 2:1) to separate both diastereoisomers of (IX) in the pure state, differing in chromatographic mobility (R_f 0.71 and 0.62).

The diastereoisomers of the 2-azetidinones (VIII) and (IX) with the greater R_f values will henceforth be designated by the letter a, and those with lower values, by the letter b. The characteristics of all the (±) and (−)-2-azetidinones (VII, VIIIa, VIIIb, IXa, and IXb) are shown in Table 1.

The IR spectra of the 2-azetidinones obtained show strong absorption at 1760-1750 cm^{-1} corresponding to carbonyl group stretching vibrations. The mass spectra of all the compounds were quite similar. Under electron impact, the 2-azetidinone molecule disintegrates in two principal ways (A and B), in agreement with literature reports [6].



The PMR spectra of optically active (−)-(IXa) and (−)-(IXb) show ring proton absorption as a typical ABX system in which $J_{AX} \approx J_{AB}$. It is well known that in 2-azetidinones the geminal constant (5-6 Hz) is approximately equal to the coupling constant (4.9-5.9 Hz) of the cis-oriented protons [7]. In the case of compounds such as (IX), these constants are 5.5-5.7 and 5.5-5.8 Hz, respectively (Table 2). In this connection, H_A absorbs as a triplet, and H_B and H_X as quartets.

In the spectra of the optically active (−)-(VIIIa) and (−)-(VIIIb), there appears a doublet for the methyl group (3-R substituent) at 1.28 and 1.22 ppm respectively. These doublets are readily distinguished in the spectra of racemic (±)-(VIIIa) and (±)-(VIIIb). The ring protons form a comples A_3BCD system which was resolved using the simulatory program SIMEQ. Similarly resolved was the ABCD system for the ring protons in (VII). The results are shown in Table 2.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument, in vaseline oil for solids or as a film for liquids; PMR spectra on Varian T-60 and XL-100 instruments, in CCl_4, internal standard MHDS (converted to TMS); and mass spectra on an MX-1303, energy 50 eV, with direct introduction of the sample into the ion source. Specific rotations were measured on an A-1 EPO instrument.

TABLE 2. ^1H Chemical Shifts (ppm relative to TMS) and Coupling Constants ^2J and ^3J (Hz) for (VII)-(IX)

Compound*	5-H	H_X	H_A	H_B	CH_3	C_6H_5	R	$^2J_{H_A-H_B}$	$^3J_{H_X-H_A}$	$^3J_{H_X-H_B}$
(±)-VII	4,74	2,69	2,92	3,10	1,48	7,25	2,68	5,2	2,5	5,2
(−)-VII	4,75	2,62	2,83	3,02	1,50	7,21	2,60	5,1	2,4	5,1
(±)-VIIIa	4,72	2,90	2,61	3,02	1,57	7,18	1,25	5,1	2,3	5,1
(±)-VIIIb	4,78	3,05	2,55	3,28	1,55	7,25	1,20	5,1	2,3	5,1
(−)-VIIIa	4,71	3,07	2,75	3,11	1,61	7,27	1,28	5,1	2,5	5,1
(−)-VIIIb	4,83	3,05	2,55	3,27	1,57	7,25	1,22	5,2	2,5	5,1
(±)-IXa	4,78	4,05	3,05	3,25	1,51	7,18	7,11	5,8	2,6	5,7
(±)-IXb	4,85	4,11	2,91	3,48	1,58	7,18	7,08	5,6	2,6	5,5
(−)-IXa	4,82	4,05	3,07	3,29	1,57	7,23	7,17	5,5	2,7	5,5
(−)-IXb	4,79	4,09	2,89	3,43	1,53	7,21	7,11	5,7	2,8	5,8

TABLE 3. 2-(α-Phenylethyl)aminoacids (IV-VI)

Compound	Mp, °C (decomp.)	Yield, %	Compound	Mp, °C (decomp.)	Yield, %
(±)-IV	>200	52	(−)-V	Viscous oil	45
(−)-IV	>195	46	(±)-VI	193—195	64
(±)-V	>150	41	(−)-VI	194—196	65

General Method of Preparation of 2-(α-Phenylethyl)aminoacids (IV-VI). A mixture of 20 mmole of the acrylic acid (I-III), 2.5 g (20 mmole) of (±)- or (−)-(S)-α-phenylethylamine with $[\alpha]_D^{20}$ = −39.1° (c 1,5, methanol) in 6 ml of dry pyridine was boiled for 2 h under reflux. After keeping for 12-14 h at room temperature, 80 ml of acetone was added, and the colorless crystals of the aminoacid (IV-VI) which separated were filtered off, and washed thoroughly (3-4 times) with acetone. The yields and melting points of these aminoacids are given in Table 3.

General Method of Preparation of 2-Azetidinones (VII-IX). To a solution of 13 mmole of the (±)- or (−)-aminoacid (IV-VI), 5.2 g (52 mmole) of $KHCO_3$, and 0.66 g (2 mmole) of tetrabutylammonium hydrogen sulfate in 14 ml of water was added 2.96 g (26 mmoles) of methanesulfonyl chloride and 52 ml of chloroform. The resulting two-phase system was stirred with a magnetic stirrer for 24 h at room temperature. Water (50 ml) was then added, and the mixture extracted with ether and the extract dried over magnesium sulfate. After removal of the ether, the residue was chromatographed on a column (silica, L 40/100, benzene–ethyl acetate, 2:1). The (±)- and (−)-2-acetidinones (VII) and the pure diastereoisomers (±)-(IXa), (±)-(IXb), (−)-(IXa), (−)-(IXb), and the diastereoisomeric pairs (±)-(VIIIa, b) and (−)-(VIIIa,b) were isolated from the column, and their analytical purity confirmed by elemental analysis. Found: C 75.1; H 7.7%. $C_{11}H_{13}NO$. Calculated: C 75.4; H 7.4%. (±)-VIIIa. Found: C 76.8; H 8.1%. $C_{12}H_{15}NO$. Calculated: C 76.2; H 7.9. (±)-(IXb). Found: C 81.0; H 7.5; N 5.4%. $C_{17}H_{17}NO$. Calculated: C 81.3; H 6.8; N 5.4%.

Separation of the diastereoisomeric mixtures (±)-(VIIIa, b) and (−)-(VIIIa, b) was carried out as follows. Plates (24 × 17 cm) with a 2-3 mm layer of Silpearl UV-254 silica gel were impregnated with methanol in a chromatographic tank. After thorough drying, 35-50 mg of the mixture of diastereoisomers in 0.5 ml of acetone was applied to the origin as a band. Elution of the plate was carried out with a 2:1 mixture of benzene and ethyl acetate up to half the height of the plate. After drying at room temperature, elution with ether was carried out twice to the full height of the plate. Under the UV lamp, two zones for the isomers of (VIIIa) and (VIIIb) could be seen, separated by a distance of 3-4 mm. Both zones were removed from the plate, and following elution with ether the diastereoisomers (VIIIa) and (VIIIb) were obtained in the pure state in a weight ratio of 1:1. In the intermediate zone between the upper and the lower, both diastereoisomers were present, and these were separated by repeated chromatography.

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SATURATED NITROGENOUS HETEROCYCLES.

10.* SYNTHESIS AND EXAMINATION OF THE STEREOISOMERS OF 3-(5-ALKYL-2-PYRROLIDYL)ALKANOLS

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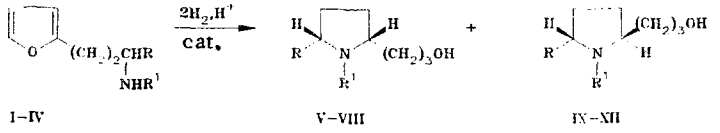
Methods have been developed for the synthesis of cis- and trans-3-(5-alkyl-2-pyrrolidyl)alkanols. The catalyst isomerization of the stereoisomers has been studied, and configurational assignments of the isomers made on the basis of x-ray structural examinations, NMR spectroscopy, and comparison of physicochemical properties. A relationship has been found between the more characteristic signals in the NMR spectra of the pyrrolidylalkanols and their spatial structures.

It has been previously reported that alkylated pyrrolidylalkanols, which are of interest for the synthesis of biologically active compounds, can be obtained by the stereochemically directed catalytic hydrogenation of the appropriate amines of the furan series in acidic media. X-ray structural analysis has shown that in the case of 5-methylpyrrolidylalkanols the principal isomer possesses the cis-configuration [1].

When the catalyst employed is nickel promoted by ruthenium [2], the formation of pyrrolidylalkanols is less stereospecific, and when an alkyl substituent is present in the 3-position of the side chain in the original amines, in addition to the cis-pyrrolidylalkanols (V-VIII), there are formed in yields up to 35% the lower-boiling trans-pyrrolidylalkanols (IX-XII).



I-IV V-VIII IX-XII

I, V, IX R=CH_3, R^1=H; II, VI, X R=R^1=CH_3; III, VII, XI R=i-C_4H_9, R^1=H; IV, VIII, XII R=i-C_4H_9, R^1=CH_3

When the reaction is carried out at 60°C under a hydrogen pressure of 60-70 atm, the ratio of the cis- and trans-isomers in the catalyzate is, according to GLC, the same throughout the reaction. At a temperature of 100°C, reversible catalytic isomerization begins, with the establishment of a constant ratio of cis- and trans-isomers, the latter predominating. The composition of the mixtures obtained is independent of temperature over the range 100-120°C. At higher temperatures, partial resinification occurs. The same ratio of isomers is established within 7-8 h in randomly selected samples, enriched in one or other of the isomers, when kept under the isomerization conditions.

*For Communication 9, see [1].

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