SATURATED NITROGEN-CONTAINING HETEROCYCLES

IV*. SYNTHESIS AND PROPERTIES OF PYRROLIDIN-2-YL- AND CYCLOALKANOPYRROLIDIN-2-YLPROPIONIC ACIDS

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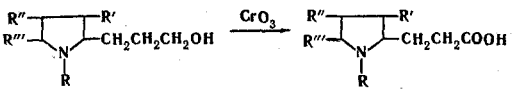
A general method for the synthesis of pyrrolidinyl- and cycloalkanopyrrolidinylpropionic acids by the oxidation of the corresponding heterocyclic alcohols has been developed. Some of those compounds have been converted into the corresponding methyl esters and pyrrolizidin-3-ones. Preliminary pharmacological tests have shown that the pyrrolizidin-3-ones possess a sedative effect.

There is information in the literature relating only to derivatives of the simplest representatives of the β-(pyrrolidin-2-yl)propionic acids [2,3]. At the same time, these acids present considerable interest as possible neurotropic agents, since they are structurally close to γ-aminobutyric acid, which plays an important role in the physiological processes of the brain.

The present paper describes a general method that we have developed for obtaining pyrrolidinyl- and cycloalkanopyrrolidinylpropionic acids by the oxidation of the corresponding pyrrolidine or cycloalkanopyrrolidine alcohols [1,4,5] with chromic anhydride in 12% sulfuric acid solution [6].

By this method we have synthesized β-(pyrrolidin-2-yl)propionic acids with alkyl substituents in various positions of the pyrrolidine ring (I-VIII) (Table 1) and also β-(cyclopentano[b]pyrrolidin-2-yl)- and β-(octahydroindol-2-yl)propionic acids (IX,X).



I–VIII

The amino acids I-X are colorless crystalline substances readily soluble in water and ethanol. The acids I-V, IX and X, having no substituent on the nitrogen atom, were converted by intramolecular acylation into the pyrrolizidin-3-ones XI-XVII (Table 2).

The esterification of the acids II, III, and VII-X with methanol in the presence of hydrogen chloride or thionyl chloride gave their methyl esters XVIII-XXIII (Table 2). In the case of acids having no substituent in position 5 of the pyrrolidine ring but possessing a hydrogen atom on the nitrogen, instead of the methyl esters the corresponding pyrrolizidin-3-ones, identical with those obtained from the acids by intramolecular acylation were obtained.

*For Communication III, see [1].

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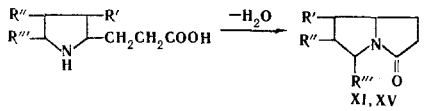
TABLE 1. β-(Pyrrolidin-2-yl)propionic Acids I-X (formulas in the text)

Compound	R	R′	R″	R‴	mp (decomp.) °C	Empirical formula	Found, %			Calculated, %			Yield %
							C	H	N	C	H	N	
I	H	H	H	H	156—157	$C_7H_{13}NO_2$	58,80 58,41	9,03 8,89	9,91 9,84	58,71	9,15	9,78	78
II	H	H	H	CH_3	160	$C_8H_{15}NO_2$	60,90 60,81	9,87 9,83	8,55 8,67	61,20	9,67	8,92	79
III	H	H	H	i-C_4H_9	157—159	$C_{11}H_{21}NO_2$	65,84 66,32	10,33 10,77	6,98 7,19	66,29	10,64	7,04	79
IV	H	H	C_2H_5	H	157—157,5	$C_9H_{17}NO_2$	63,10 62,95	9,67 10,09	8,30 8,47	63,21	10,02	8,19	60
V	H	H	i-C_3H_7	H	162	$C_{10}H_{19}NO_2$	64,40 64,52	10,30 10,26	7,80 7,93	64,76	10,34	7,56	65
VI	H	i-C_3H_7	H	CH_3	155—156	$C_{11}H_{21}NO_2$	65,82 65,93	10,45 10,75	7,14 6,95	66,29	10,64	7,04	48
VII*	CH_3	H	H	H	155	$C_8H_{15}NO_2 \cdot HCl$	50,50 50,30	8,40 8,48	7,02 6,91	49,78	8,36	7,26	65
VIII*	CH_3	H	C_2H_5	H	104—105	$C_{10}H_{18}NO_2 \cdot HCl$	54,02 53,60	8,77 8,64	5,96 6,32	54,10	8,64	6,32	77
IX	—	—	—	—	194—195	$C_{10}H_{17}NO_2$	65,24 65,53	9,53 9,55	7,66 8,04	65,54	9,35	7,64	85
X	—	—	—	—	186—187	$C_{11}H_{19}NO_2$	66,54 66,70	9,39 9,50	7,49 7,40	66,97	9,71	7,10	83

*Isolated in the form of the hydrochlorides.

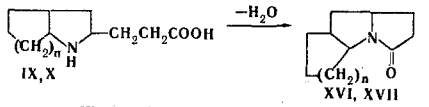
TABLE 2. The Pyrrolizidin-3-ones (XI-XVII) and the Methyl β-(Pyrrolidin-2-yl)propionates (XVIII-XXIII).

Compound	Obtained from	bp, °C (pressure mm)	n_D^{20}	d_4^{20}	MR_D Found	MR_D Calculated	Empirical formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
XI	I	115 (10)	1,4980	1,0729	34,23	34,08	$C_7H_{11}NO$	66,69 66,95	9,00 8,70	11,66 11,69	67,16	8,87	11,21	81
XII	II	117 (10)	1,4910	1,0520	38,37	38,79	$C_8H_{13}NO$	69,42 69,26	9,63 9,36	10,32 10,02	69,12	9,43	10,08	80
XIII	III	139 (10)	1,4842	0,9925	52,30	52,55	$C_{11}H_{19}NO$	72,77 72,55	10,52 10,49	8,04 7,89	72,88	10,52	7,74	66
XIV	IV	133 (10)	1,4880	1,0249	43,15	43,31	$C_9H_{15}NO$	70,09 70,10	9,94 9,80	9,46 9,28	70,53	9,88	9,13	78
XV	V	141 (10)	1,4849	1,0070	47,58	47,93	$C_{10}H_{17}NO$	71,84 71,61	12,01 11,89	8,01 7,96	71,92	12,07	8,39	75
XVI	IX	126 (3)	1,5190	1,0980	45,70	45,73	$C_{10}H_{15}NO$	72,40 72,22	9,26 9,18	8,08 8,32	72,70	9,15	8,47	70
XVII	X	141 (3)	1,5175	1,0800	50,26	50,36	$C_{11}H_{17}NO$	73,50 73,60	9,71 9,62	7,82 7.80	73,70	9,56	7,81	50
XVIII	II	92 (8)	1,4570	0,9889	47,16	46,81	$C_9H_{17}NO_2$	62,94 62,97	9,73 9,95	7,60 7,75	63,10	10,02	8,19	52
XIX	VII	90—91 (10)	1,4510	0,9819	46,84	47,16	$C_9H_{17}NO_2$	62,70 62,83	10,03 10,10	7,94 7,90	63,10	10,02	8,19	36
XX	VIII	105 (6)	1,4520	0,9567	56,20	56,40	$C_{11}H_{21}NO_2$	66,70 66,86	10,65 10,96	6,51 6,80	66,36	10,62	7,00	39
XXI	III	102 (3)	1,4598	0,9642	60,57	60,67	$C_{12}H_{23}NO_2$	68,07 68,01	10,33 10,89	6,04 6,52	67,57	10,86	6,56	60
XXII	IX	101—102 (2)	1,4800	1,0390	53,63	53,85	$C_{11}H_{19}NO_2$	66,95 66,53	10,00 9,71	7,01 6,88	66,97	9,71	7,10	49
XXIII	X	115 (2)	1,4852	1,0370	58,48	58,37	$C_{12}H_{21}NO_2$	68,49 68,12	10,14 10,00	6,51 6,45	68,21	10,01	6,63	30



XI, XV

XI $R'=R''=R'''=H$; XII $R'=R''=H$, $R'''=CH_3$; XIII $R'=R''=H$, $R'''=i\text{-}C_4H_9$; XIV $R'=R'''=H$, $R''=C_2H_5$; XV $R'=R'''=H$, $R''=i\text{-}C_3H_7$



XVI, XVII

IX $n=1$; X $n=2$; XVI $n=1$; XVII $n=2$

In the IR spectra of the acids I-VI, IX, and X there is a strong absorption band in the 1550-1640 cm^{-1} region corresponding to an ionized carboxy group. In the hydrochlorides of the acids VII and VIII, these bands have disappeared and have been replaced by carbonyl absorption bands (1700-1725 cm^{-1}). In the spectra of the pyrrolizidin-3-ones, there is a strong band at 1675-1677 cm^{-1} corresponding to the stretching vibrations of the C=O bond in cyclic γ-lactams, and in compounds XVIII-XXIII there is one at 1746-1754 cm^{-1} (C=O in esters).

Pharmacological tests carried out in the All-Union Institute for Experimental Medicine, AMS USSR, have shown that the acids I-X have little activity, while the pyrrolizidin-3-ones exhibit a selective action on the central nervous system the nature and degree of which depend on the structure and the dose of the substances. Compounds XIII-XVI possess a well-marked sedative effect [7].

EXPERIMENTAL

β-(5-Isobutylpyrrolidin-2-yl)propionic Acid (III). With stirring, a solution of 1.4 g (0.014 mole) of chromic anhydride in 42 ml of 12% sulfuric acid was added to a solution of 1.85 g (0.01 mole) of 1-(5-isobutylpyrrolidin-2-yl)propan-3-ol in 20 ml of water. The reaction mixture was left for an hour and was then treated with a hot solution of 24 g (0.076 mole) of barium hydroxide in 60 ml of water. The precipitate was filtered off, and the filtrate was treated with dry ice and again filtered. The water was distilled off, the residue was dissolved in 30 ml of absolute ethanol, the solution was filtered, the ethanol was distilled off, and the residual vitreous mass was triturated with ether, whereupon colorless cyrstals deposited which were recrystallized from a mixture of ethanol and acetone. Yield of III 1.57 g (79%).

The acids I, II, IV-VI, IX, and X were obtained similarly (see Table 1).

β-(1-Methylpyrrolidin-2-yl)propionic acid (VII) and β-(4-ethyl-1-methylpyrrolidin-2-yl)propionic acid acid (VIII) were isolated in the form of the hydrochlorides by treating the corresponding unpurified acids with the calculated amount of hydrochloric acid. The hydrochlorides were recrystallized from isoamyl alcohol.

4-Methylpyrrolizidin-3-one (XII). A distillation flask heated in a metal bath (bath temperature 180°C) was charged with 3 g of β-(5-methylpyrrolidin-2-yl)propionic acid (II). After the acid had melted, the pressure was lowered to 100 mm, and the water formed was distilled off. Then the pressure was lowered to 10 mm and the liquid remaining in the flask was distilled. The distillate was dissolved in ether and dried with $MgSO_4$. Vacuum distillation yielded 2.2 g (80%) of XII.

The pyrrolizidones XI and XIII-XVII were obtained similarly; they formed colorless mobile liquids readily soluble in ether and ethanol (see Table 2).

Methyl β-(5-methylpyrrolidin-2-yl)propionate (XVIII). A. A solution of 5 g of the acid II in 100 ml of a 3 N solution of hydrogen chloride in absolute methanol was boiled for 3 hr 30 min. The methanol was distilled off, the residue was dissolved in 5 ml of water and treated with 50 ml of ethyl acetate, and 5 g of potassium carbonate was rapidly added. The ethyl acetate layer was separated off and dried with $MgSO_4$. The solvent was driven off and the residue was distilled in vacuum. The yield of XVIII was 2.8 g (52%).

The esters XIX-XIII were obtained similarly (see Table 2).

B. With stirring, 4.76 g (0.04 mole) of thionyl chloride was added through a reflux condenser to a solution of 6.28 g (0.04 mole) of II in 20 ml of absolute methanol. The reaction mixture was left for 1 hr,

and then the solvent was distilled off. The residue was dissolved in 25 ml of methanol and this solution was treated with 10 ml of methanol containing 2.16 g (0.04 mole) of sodium methoxide. The precipitate was filtered off. After alcohol had been distilled off, a fraction with bp 92°C (8 mm) was collected. The yield of XVIII was 3.5 g (50%).

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