SATURATED NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

III. Synthesis and Properties of 5-Alkylpyrrolidones-2*

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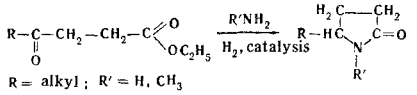
A number of previously unknown 5-alkylpyrrolidones-2 and 1-methyl-5-alkylpyrrolidones-2 were synthesized by reductive amination of the ethyl esters of 8-ketocarboxylic acids with ammonium and methylamine in the presence of Raney nickel, ruthenium dioxide, or Raney nickel activated with ruthenium. The highest yields of 5-alkylpyrrolidones-2 were obtained when ruthenium dioxide was used as a catalyst. The acetyl derivatives of 5-alkylpyrrolidones-2 are described.

The 5-alkylpyrrolidones-2 are of interest as potential physiologically active substances [2–5].

The following methods are most often used in order to obtain pyrrolidones-2: the interaction of γ-lactones with amminium or amines [6–7], the reaction between succinimide and Grignard reagent [8–9], and also the reduction of esters of nitrocarboxylic acids to ester of γ-amino acids with subsequent cyclization [10].

In order to synthesize the 5-alkylpyrrolidones-2, we used the method of reductive amination of ethyl esters of γ-ketocarboxylic acids.



Original esters of γ-ketocarboxylic acids were obtained from furyl-alkyl carbinols, synthesized in turn during the interaction between furol and alkylmagnesium halides [11–13].

Ethyl esters of γ-ketocarboxylic acids are converted into 5-alkyl-pyrrolidones-2 and 1-methyl-5-alkylpyrrolidones-2 under the conditions of the hydroamination reaction with yields up to 75% of the theoretical values. The reaction is conducted in a rotating autoclave on heating to 120° C, with a hydrogen pressure of 80–140 atm in the presence of the catalysts, Raney nickel, ruthenium dioxide, or Raney nickel activated with ruthenium. The ethyl ester of the γ-keto acid and ammonium or methylamine were introduced into the reaction mixture in the ratio of 1 : 3. The solvents were methyl or ethyl alcohol. When ruthenium dioxide was used as the catalyst, the yield of alkyl pyrrolidones was greater than in the presence of Raney nickel or Raney nickel activated with ruthenium.

The mechanism of formation of 5-alkylpyrrolidones-2 from ethyl esters of γ-ketocarboxylic acids under conditions of reductive amination is discussed in Shuikin et al. [14]. According to these authors, the mechanism involves intermediate formation of the amides of γ-ketocarboxylic acids with their subsequent dehydration, hydrogenation, and cyclization. However, it is possible to propose another mechanism for this reaction in which amination of the keto group initially occurs according to the general scheme of reductive amination [15] with subsequent dehydration, hydrogenation, and cyclization.

The 5-alkylpyrrolidones are amorphous fusible substances. The lower homologs are readily soluble in water. With increase in the alkyl radical the solubility in water decreases. They are readily soluble in methyl and ethyl alcohols. The 5-alkylpyrrolidones-2 are readily acetylated on boiling with twice the theoretical quantity of acetic anhydride.

The 1-methyl-5-alkylpyrrolidones are colorless liquids insoluble in water and readily soluble in alcohol.

Physical constants and data of the analysis of alkylpyrrolidones-2 and acetyl derivatives of certain of them are presented in Tables 1–3.

In the IR spectra of 5-alkylpyrrolidones-2 absorption bonds are found at 1705 and 1715 cm^{-1} corresponding to valency oscillations of the C=O group and also at 3100 and 3200 cm^{-1} corresponding to valency oscillations of the NH group. On substitution of the hydrogen atom at nitrogen by the methyl radical in molecules of 5-alkylpyrrolidones-2 the band of the valency oscillation of the NH group disappears, and frequency of the valency oscillation of the C=O group essentially does not change in value (1715–1720 cm^{-1}).

The 5-alkylpyrrolidones-2 develop a well-known activity against both gram-positive and gram-negative species of microorganisms. The minimal bacteriostatic concentration of 5-propyl-pyrrolidone-2 in relation to B. coli is 10 μg/ml and in relation to St. aureus is 100 μg/ml. With increase in the alkyl radical the antimicrobial activity decreases. The most active of the acetylated 5-alkylpyrrolidones-2 was found to be 1-acetyl-5-hexylpyrrolidone-2, which inhibits the growth of the golden staphylococcus at a concentration of 75 μg/ml. The 1-methyl-5-alkyl-pyrrolidones-2 possess no antimicrobial activity.

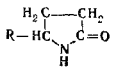
Studies of the physiological activity conducted in the Institute of Experimental Medicine, Academy of Sciences of the USSR by E. V. Moreva, showed that the 5-alkylpyrrolidones-2 have a certain sedative action. These studies are being continued.

EXPERIMENTAL

The ethyl esters of γ-ketocarboxylic acids, including γ-ketohexanic (I), γ-ketoheptanic (II), γ-ketooctanic (III), γ-ketoisooctanic (IV), γ-ketononanic (V), γ-ketoisononanic (VI), γ-ketodecanic (VII), γ-ketoisodecanic (VIII), γ-ketoundecanic (IX), γ-ketotridecanic (X) and γ-ketoheptadecanic (XI) acids were obtained by previously described methods [11, 12].

*For part II, see [1].

Table 1

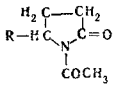


Compound	R	Obtained from	Catalyst*	Boiling point, °C (pressure, mm)	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
XII	C_2H_5**	I	NiR	127—130 (7)	$C_6H_{11}NO$	—	—	—	—	—	—	62.1
XIII	C_3H_7	II	NiR		$C_7H_{13}NO$	65.90	9.99	11.01	66.06	10.23	11.02	62.2
			NiR(Ru)	105—106 (1)		65.88	10.16	10.94				68.7
			RuO_2									74.4
XIV	C_4H_9	III	NiR	118—120 (1)	$C_8H_{15}NO$	68.36	10.24	10.46	68.08	10.63	9.93	60.2
			NiR(Ru)			68.07	10.65	10.01				68.0
			RuO_2									75.0
XV	*i*-C_4H_9	IV	NiR	119—120 (1)	$C_8H_{15}NO$	67.93	10.41	10.10	68.08	10.63	9.93	69.1
XVI	C_5H_{11}	V	NiR		$C_9H_{17}NO$	69.42	10.99	8.69	69.67	10.96	9.03	68.4
			NiR(Ru)	126—128 (1)		69.54	10.96	9.04				67.1
			RuO_2									73.6
XVII	*i*-C_5H_{11}	VI	NiR	148—150 (5)	$C_9H_{17}NO$	69.98	11.09	9.09	69.67	10.96	9.03	60.3
						69.96	11.29	8.98				
XVIII	C_6H_{13}	VII	NiR	164—165 (7)	$C_{10}H_{19}NO$	71.00	11.35	8.22	71.07	11.24	8.28	59.5
						71.07	11.44	8.28				
XIX	*i*-C_6H_{13}	VIII	NiR	150—151 (4)	$C_{10}H_{19}NO$	71.35	11.47	8.04	71.07	11.24	8.28	63.3
						71.28	11.39	8.27				
XX	C_7H_{15}	IX	NiR	154—157 (2)	$C_{11}H_{21}NO$	72.18	11.38	7.30	72.13	11.47	7.67	64.4
						72.01	11.45	7.28				
XXI	C_9H_{19}	X	NiR	159—161 (1)	$C_{13}H_{25}NO$	73.82	11.94	6.46	74.00	11.94	6.64	67.4
						73.72	12.00	6.73				
XXII	$C_{13}H_{27}$	XI	RuO_2	[Tmp 63—64°]	$C_{17}H_{33}NO$	77.05	12.13	5.56	76.92	12.31	5.23	76.6
						77.12	12.24	5.40				

*NiR, Raney nickel: NiR(Ru), Raney nickel activated with ruthenium.

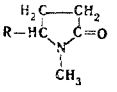
**Data in the literature [16]: Bp 130° C (8 mm), n_D^{20} 1.4800.

Table 2



R	Bp, °C (pressure, mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
C_2H_5	103—105 (7)	1.4733	$C_8H_{13}NO_2$	61.93	9.00	8.90	61.99	8.45	9.04	80.7
C_3H_7	108—109 (7)	1.4704	$C_9H_{15}NO_2$	63.84	9.02	8.26	63.96	8.95	8.29	83.4
C_4H_9	108—109 (6)	1.4690	$C_{10}H_{17}NO_2$	65.21	9.42	8.08	65.63	9.36	7.70	86.2
C_5H_{11}	111—112 (7)	1.4687	$C_{11}H_{19}NO_2$	66.94	10.02	6.93	67.06	9.72	7.11	79.2
i-C_5H_{11}	113—115 (6)	1.4680	$C_{11}H_{19}NO_2$	66.86	9.89	7.00	67.06	9.72	7.11	82.0
C_6H_{13}	112—113 (7)	1.4631	$C_{12}H_{21}NO_2$	69.15	10.34	6.45	69.30	10.03	6.64	85.5
C_9H_{19}	170—171 (7)	1.4602	$C_{15}H_{27}NO_2$	70.96	10.45	5.27	71.21	10.76	5.54	83.8

Table 3



R	Bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
				found	calculated		C	H	N	C	H	N	
C_3H_7	75—76 (1)	1.4706	0.9705	40.64	40.89	$C_8H_{15}NO$	68.18 68.26	10.50 10.64	10.01 10.05	68.08	10.63	9.93	61.7
C_4H_9	92—94 (1)	1.4695	0.9558	45.22	45.52	$C_9H_{17}NO$	69.41 69.58	10.70 10.74	9.31 9.33	69.67	10.96	9.03	60.0
C_5H_{11}	100—102 (1)	1.4680	0.9462	49.75	50.13	$C_{10}H_{19}NO$	71.05 71.17	11.06 11.22	8.19 8.14	71.07	11.24	8.28	67.1
i-C_5H_{11}	97—99 (3)	1.4690	0.9490	49.67	50.13	$C_{10}H_{19}NO$	71.08 71.16	11.36 11.45	8.35 8.48	71.07	11.24	8.28	64.7
C_6H_{13}	150—153 (6)	1.4654	0.9321	54.55	54.74	$C_{11}H_{21}NO$	72.22 72.35	11.40 11.52	7.57 7.89	72.13	11.47	7.67	65.4

5-Propylpyrrolidone-2 (XIII). A) A 24 g quantity of the ethyl ester of γ-ketoheptanic acid (II), 50 ml methyl alcohol saturated with ammonia, and 3 g Raney nickel were placed in a rotating autoclave 150 ml in volume, and hydrogen was introduced at a pressure of 90 atm. The reaction was conducted with constant stirring of the reaction mixture at 120° C until hydrogen ceased to be absorbed (4 hr). At the end of the reaction the hydrogenate was liberated from the catalyst by filtration or centrifugation, methyl alcohol and ammonia were removed by distillation, and the residue was sublimed at reduced pressure, a fraction separating with a Bp of 105–106° C (1 mm). Yield, 11 g (62.2%). On storage the compound crystallized and has a mp of 35–36° C.

B) When the reaction proceeds in the presence of 1 g of ruthenium dioxide, a hydrogen pressure of 60 atm and heating to 110–120° C, 13.4 g of 5-propylpyrrolidone (74.4%) were obtained.

C) When 3 g of Raney nickel activated with ruthenium were used as a catalyst the yield of 5-propylpyrrolidone-2 was 12.4 g (68.7%).

By an analogous method the 5-ethyl derivative (XII) was obtained from compound I, the 5-butyl derivative (XIV) was obtained from compound III, the 5-iso-butyl derivative (XV) was obtained from compound IV, the 5-amyl derivative (XVI) was obtained from compound V, the 5-iso-amyl derivative (XVII) was obtained from compound VI, the 5-hexyl derivative (XVIII) was obtained from compound VII, the 5-heptyl derivative (XX) was obtained from compound IX, the 5-nonyl derivative (XXII) was obtained from compound X, and 5-tridecyl-pyrrolodone-2 (XXIII) was obtained from compound XI (Table 1).

1-Acetyl-5-propylpyrrolidone-2 was obtained by boiling 4 g of 5-propylpyrrolidone-2 (XIII) with 7 g of acetic anhydride for 90 min and with subsequent distillation at reduced pressure. Yield, 4.42 g (80.7%), Bp 108–109° C (7 mm), n_D^{20} 1.4704.

By an analogous method the acetylated derivatives of certain other 5-alkylpyrrolidones-2 (Table 2) were obtained.

1-Methyl-5-propylpyrrolidone-2. A 17.2 g quantity of compound II, 1.7 g Raney nickel, and 60 ml of a 20% solution of methylamine in methyl alcohol were introduced into a rotating autoclave 150 ml in volume. Hydrogen was introduced into the autoclave at a pressure of 90 atm. The reaction was conducted on heating to 120–130° C until absorption of hydrogen ceased. The catalyst, excess methylamine, and solvent were then removed, and the residue was sublimed at reduced pressure. Yield, 8.6 g (61.7%). Bp 75–76° C (7 mm).

The other 1-methyl-5-alkylpyrrolidones-2 were obtained in an analogous manner (Table 3).

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