was used as the titrating agent. The concentration of the free base in the titrated solution at the half-neutralization point was ~0.015 g-equivalent/liter. Diphenylguanidine was used as the standard substance in the determination of the ΔpK_a values.

LITERATURE CITED

1. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 348 (1976).
2. E. E. Mikhlina, A. D. Yanina, T. S. Loseva, K. F. Turchin, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 7, 977 (1974).
3. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 2, 209 (1976).
4. W. Z. F. Armarego, J. Chem. Soc., B, 191 (1966).
5. L. M. Alekseeva, G. G. Dvoryantseva, Yu. N. Sheinker, A. A. Druzhinina, R. M. Palei, and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 1, 70 (1976).
6. M. I. Struchkova, G. G. Dvoryantseva, T. P. Belova, Yu. E. Sklyar, and R. P. Evstigneeva, Khim. Geterotsikl. Soedin., No. 11, 1498 (1973).

SYNTHESIS OF 1-PHENYL-3-METHYL-4-ALKYL-4-[N-METHYLBUTYRO(CAPRO)LACTYL]-5-PYRAZOLONES

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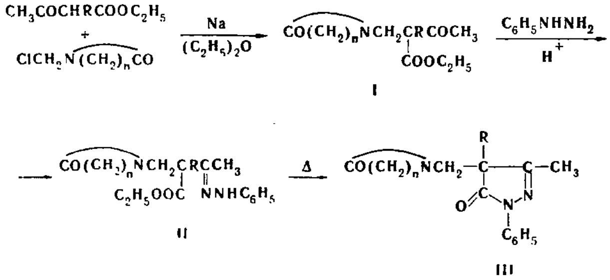
The corresponding hydrazones, which on heating are cyclized to give 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(2-oxopyrrolidinomethyl)- and 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(N-methylcaprolactyl)pyrazolones, are formed in the reaction of alkyl(benzyl)(2-oxopyrrolidinomethyl)- and alkyl(benzyl)(N-methylcaprolactyl)acetoacetic esters with phenylhydrazine.

5-Pyrazolones with lactam rings in the side chain are unknown. Since the lactam ring increases the complexing ability, the hydrophilic character, the dye affinity, the solubility, and the biological activity [1-6], a study of the reaction of phenylhydrazine with ethyl alkyl(benzyl) (2-oxopyrrolidinomethyl)- and alkyl(benzyl)(N-methylcaprolactyl)acetoacetates (Table 1) seemed of definite interest. The latter were obtained from N-(α-chloroalkyl)lactams, in view of the lability of their halogen atoms [6, 7]. Intense bands at 1733 (ester C=O), 1712 (ketone C=O), and 1692 cm^{-1} (lactam C=O) are observed in the IR spectra of these compounds.



I—III a n=3, R=C_4H_9; b n=3, R=C_5H_{11}; c n=3, R=$CH_2C_6H_5$; d n=5, R=C_4H_9; e n=5, R=C_5H_{11}; f n=5, R=$CH_2C_6H_5$

Esters I react with phenylhydrazine in an equimolar ratio at room temperature in the presence of one to two drops of glacial acetic acid to give corresponding hydrazones II. Their IR spectra contain characteristic

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TABLE 1. Esters I

Compound	bp, °C (mm)	R_f	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calc., %			Yield, %
					found	calc.		C	H	N	C	H	N	
Ia	160(2)	0,65	1,0708	1,4770	74,88	74,68	$C_{15}H_{25}O_4$	63,6	9,1	5,2	63,5	9,0	5.6	89
Ib	165—167(2)	0,65	1,0667	1,4780	78,82	79,50	$C_{16}H_{27}O_4$	64,3	9,3	5,3	64,7	9,1	4,7	72
Ic	200(2)	0,64	1,1470	1,5260	84,84	85,14	$C_{18}H_{23}O_4$	68,0	7,6	4,8	68,1	7,2	4,4	71
Id	173—175(2)	0,61	1,0620	1,4850	83,93	84,12	$C_{17}H_{29}O_4$	65,3	9,8	5,0	65,7	9,3	4,5	65
Ie	178—179(2)	0.60	1,0498	1,4850	88,84	88,74	$C_{18}H_{31}O_4$	65.8	10,0	4.7	66,3	9,5	4,3	92
If	203(2)	0,59	1,1291	1,5271	94,04	93,37	$C_{21}H_{27}O_4$	69,4	8,2	4,4	69,4	7,8	4,0	62

TABLE 2. Phenylhydrazones II

Compound	mp, °C	R_f	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIa	134—136	0,41	$C_{21}H_{31}O_3N_3$	67,0	8,9	10,8	67,5	8,3	11,2	78
IIb	126—128	0,37	$C_{22}H_{33}O_3N_3$	67,7	9,0	10,7	68,2	8,5	10,8	69
IIc	136	0,36	$C_{24}H_{29}O_3N_3$	70,5	7,6	10.6	70.7	7,1	10,3	71
IId	119—121	0.43	$C_{23}H_{35}O_3N_3$	68,5	9,0	10,2	68.8	8,7	10,4	51
IIe	132—134	0,43	$C_{24}H_{37}O_3N_3$	69,5	9,3	10,4	69,3	8,9	10,1	63
IIf	146—148	0,42	$C_{26}H_{33}O_3N_3$	72,0	7,0	9,7	71,7	7,5	9,6	51

TABLE 3. Pyrazolones III

Compound	mp, °C	R_f	n_D^{20}	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIIa	68—70	0,23	—	$C_{19}H_{25}O_2N_3$	70,0	7,9	13,0	69,7	7,6	12,8	40
IIIb	60	0,19	—	$C_{20}H_{27}O_2N_3$	70,6	8.5	12,5	70,3	7,9	12,3	58
IIIc	—	0,18	1,5680	$C_{22}H_{23}O_2N_3$	72,9	6,8	11,0	73,1	6,3	11,3	60
IIId	84—86	0,18	—	$C_{21}H_{29}O_2N_3$	71,3	8,6	12,0	70,9	8,1	11,8	80
IIIe	—	0,18	1,5330	$C_{22}H_{31}O_2N_3$	71,3	9,0	11,4	71,5	8,4	11,3	58
IIIf	—	0,17	1,5670*	$C_{24}H_{27}O_2N_3$	74,3	7,3	11,0	74,0	6,8	10,7	48

* This is the n_D^{40} value.

absorption bands for ester (1726) and lactam (1668) carbonyl groups, the C = N double bond (1592), the phenyl group (1603), and the NH group (3350 cm^{-1}).

The hydrazones undergo cyclization at 200-230°C (15 mm) with the liberation of ethanol to give 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(2-oxopyrrolidinomethyl)- and 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(N-methylcaprolactyl)-5-pyrazolones(III). Characteristic absorption frequencies for a lactam carbonyl group (1692 cm^{-1}) and for a phenyl group (1603 cm^{-1}) are observed in the IR spectra of III.

As a result of primary testing of the biological activity of II and III, a pronounced antiphlogistic and analgetic effect was observed for most of them.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were recorded with an IKS-14 spectrometer. Chromatography in a thin layer of loose activity II Al_2O_3 was carried out in the following solvent systems: CCl_4–dioxane–methanol (16 : 4 : 1) for I, $CHCl_3$–acetone (7 : 3) for II, and $CHCl_3$–acetone (50 : 1) for III.

Alkyl(benzyl)(2-oxopyrrolidinomethyl)- and Alkyl(benzyl)-N-methylcaprolactyl)acetoacetic Esters (I). A 1-mole sample of alkyl(benzyl)acetoacetic ester was added with cooling to 23 g of sodium in 350 ml of ether, and the reaction mixture was refluxed for 40 min until the sodium dissolved completely. A 1.05-mole sample of the appropriate N-chloromethyllactam was then added with stirring and cooling, and the mixture was heated until it was neutral. The resulting salt was dissolved in the minimum amount of water. The ether layer and the ether extract of the aqueous layer were dried over Na_2SO_4, the ether was removed, and the residue was vacuum fractionated. The physicochemical constants of the synthesized compounds are presented in Table 1.

Hydrazones II. An equimolar mixture of the appropriate ester I and phenylhydrazine was allowed to stand in the presence of one to two drops of CH_3COOH for 3 days at room temperature, and the resulting crystals were recrystallized from aqueous ethanol. The physicochemical constants of II are presented in Table 2.

5-Pyrazolones (III). Pyrazolones II were heated at 200-230° (15 mm), during which the alcohol liberated during the cyclization condensed in a trap. Those reaction products that solidified after cooling were recrystallized from petroleum ether. The remaining compounds were obtained as very viscous liquids. The physicochemical constants of the synthesized compounds are presented in Table 3.

LITERATURE CITED

1. M. F. Shostakovskii, F. P. Sidel'kovskaya, and M. G. Zelenskaya, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1457 (1957).
2. M. F. Shostakovskii, F. P. Sidel'kovskaya, and A. M. Khomutov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 919 (1955).
3. W. Reppe, Polyvinylpyrrolidon, Verlag Chemie, Weinheim (1954).
4. M. F. Shostakovskii and F. P. Sidel'kovskaya, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 111 (1958).
5. F. P. Sidel'kovskaya, M. G. Zelenskaya, and M. F. Shostakovskii, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 901 (1959).
6. M. F. Shostakovskii, F. P. Sidel'kovskaya, É. V. Rogova, F. L. Kolodkin, and F. Ibragimov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1111 (1961).
7. É. G. Mesropyan, Yu. A. Bunyatyan, R. K. Aliev, and M. T. Dangyan, Khim. Geterotsikl. Soedin., No. 1, 22 (1974).

RESEARCH IN THE IMIDAZOLE SERIES

LXXXIX.* REACTION OF 1-ALKYL-2-CYANO(ALKOXYCARBONYL)METHYL DERIVATIVES OF IMIDAZOLE AND BENZIMIDAZOLE WITH α-HALO KETONES

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The reaction of 1-alkyl-2-cyano(alkoxycarbonyl)methyl derivatives of imidazole and benzimidazole with α-halo ketones was studied. It was established that the presence of electron-acceptor substituents (CN, $COOC_2H_5$) in the methyl group in the 2 position of the imidazole ring markedly facilitates cyclization of the intermediate imidazolium and benzimidazolium halides to the corresponding cyano (alkoxycarbonyl) derivatives of pyrrolo[1,2-a]imidazoles and pyrrolo[1,2-a]benzimidazoles.

We have established that the reaction of 1-alkyl-2-cyano(alkoxycarbonyl)methyl derivatives of imidazole and benzimidazole with α-halo ketones, which opens up a route to the synthesis of the previously undescribed carboxylic acid derivatives of the pyrrolo[1,2-a]imidazole and pyrrolo[1,2-a]benzimidazole series, does not always proceed unambiguously, in contrast to the analogous reaction in the case of 1,2-dialkyl-substituted imidazoles and benzimidazoles [1]. In some cases quaternary salts, which are readily cyclized to 7-cyano derivatives of pyrrolo[1,2-a]imidazole (IX-XI) without the application of an alkaline agent when they are refluxed in water, are formed when 2-cyanomethyl derivatives of imidazole (I, II) are heated with α-halo ketones in acetone. Treatment with an alcohol solution of sodium ethoxide in the cold was necessary only for the cyclization of bromide VII.

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*See [6] for communication LXXXVIII.

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