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THE GENERAL SYNTHESIS OF 3-ALKYLIDENE-2,5-PIPERAZINEDIONES

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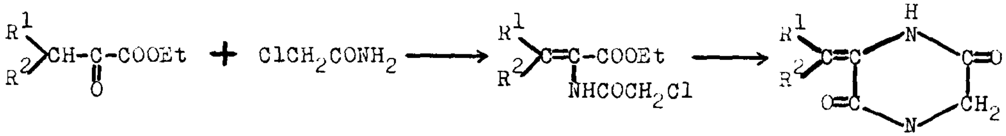
Up to the present, only a few 3-monoalkylidene-2,5-piperazinediones (II) have been appeared in literatures. Bergmann[1)], and others[2,3)] have synthesized 3-methylidene derivative from glycylserine by halogenation and amination. One of the present authors succeeded in preparation of 3-isopropylidene derivative[4)] via ethyl 2-chloroacetamido-3-methyl-2-butenoate (Ic) obtained by reaction of dehydrovaline ethylester with chloroacetic acid chloride. In addition, 3-isobutylidene derivative[5)] was synthesized via the corresponding 2-pentenoate (If) derived from esterification of the free acid. Recently, Dominy et al[6)] and Porter et al[7)] reported the preparation of 3-benzylidene derivative by a similar method mentioned above. Consequently, N-chloroacetyldehydro-amino acid esters (I) seems to be the most suitable intermediate to obtain 3-monoalkylidene (II) derivatives.

In this paper, we wish to communicate a simple procedure to synthesize I as illustrated in Scheme 1. Various 3-monoalkylidene derivatives were prepared through these intermediates.



Scheme 1 (I) (II)

a) R^1=R^2=H; b) R^1=CH_3, R^2=H; c) R^1=R^2=CH_3; d) R^1=C_2H_5, R^2=H;
e) R^1=n-C_3H_7, R^2=H; f) R^1=i-C_3H_7, R=H

We have examined the effect of various acidic catalysts during the condensation of equimolar amount of ethyl 2-oxocarboxylate and chloroacetamide in refluxed dry benzene[8]. It was found that , among catalysts tested, concentrated sulfuric acid and phosphoroxichloride were effective, and I was obtained in fairly good yield, as was shown in Table 1.

Table 1

Preparation of ethyl 2-(2-chloroacetamido)-2-pentenoate in the presence of various catalysts[a]

Catalyst	ml(g)	Reaction time (hr)	Yield (%)	Catalyst	ml(g)	Reaction time (hr)	Yield (%)
conc. H_2SO_4	5	3	6	$POCl_3$	3	4	27
"	2	12	36	"	3	5	34
"	1	12	50	"	1	8	42
"	1	18	66	P_2O_5	(4)	8	0
"	1	24	59	H_2PO_4	3	8	0
fuming H_2SO_4[b]	(2)	8	34	TosH[c]	(2)	8	14
"	(1)	8	45	DCC[d]	(10.3)	8	0

a) Mixture of ethyl 2-oxopentanoate (50 mmol) and chloroacetamide (50 mmol) was refluxed in dry benzene (50 ml). b) 30% of SO_3. c) p-Toluenesulfonic acid. d) Dicyclohexylcarbodiimide.

When cooled ethanol solution of I was saturated with dry ammonia and then allowed to stand for a day at room temperature, cyclization reaction was occurred gradually to deposited colorless amorphous crystals. The crystals were recrystallized from boiling water to give II in pure state. The structure of I and II were established by elementary analyses, IR and UV spectra. These results were summarized in Tables 2 and 3.

The above success in preparation of II permited us easy to synthesize various unsymmetrical 3,6-dialkylidene- and 3-alkylidene-6-arylidene-2,5-piperazinediones by condensation of II with alkyl- or arylaldehyde. These detailed results will be published elswhere.

Table 2. Ethyl 2-(2-chloroacetamido)-2-alkenoates (I)[a)]

Compds	Bp. °C/mmHg (mp. °C)	Yield (%)	Formula	Found,% C	Found,% H	Found,% N	Calcd,% C	Calcd,% H	Calcd,% N	IR: ν_{NaCl} cm^{-1}
Ia	86-87/1.5	24	$C_7H_{10}NO_3Cl$			7.02			7.31	3340, 1720, 1680, 1525
Ib	120-122/2	46	$C_8H_{12}NO_3Cl$	46.57	5.98	6.58	46.49	6.30	6.78	3250, 1725, 1675, 1530
Ic[4)]	(117-118)	58	$C_9H_{14}NO_3Cl$	48.78	6.71	6.34	48.98	6.80	6.35	3250, 1720, 1665, 1540
Id	121-123/2	42	$C_9H_{14}NO_3Cl$	48.52	6.75	6.09	48.98	6.80	6.35	3250, 1725, 1670, 1525
Ie	132-134/2	45	$C_{10}H_{16}NO_3Cl$	51.57	7.49	5.83	51.61	7.31	6.02	3250, 1730, 1665, 1525
If[5)]	133-135/3	37	$C_{10}H_{16}NO_3Cl$	51.51	7.29	6.13	51.61	7.31	6.02	3250, 1720, 1660, 1520

a) Ethyl 2-oxocarboxylates (50 mmol) were refluxed in the presence of $POCl_3$ (1 g) in benzene (50 ml) for 8 hr.

Table 3. 3-Alkylidene-2,5-piperazinediones (II)

Compds	Mp. °C[a)]	Yield (%)	Formula	Found,% C	Found,% H	Found,% N	Calcd,% C	Calcd,% H	Calcd,% N	IR: ν_{KBr} cm^{-1}	UV: $\lambda_{\text{nm}}^{H_2O}$ ($\varepsilon \times 10^{-3}$)
IIb	285-286	55	$C_6H_8N_2O_2$	51.38	5.82	19.67	51.42	5.75	19.99	3180, 3060, 1690, 1670, 1635	218(13.8) 238(11.9)
IIc[4)]	260-261	58	$C_7H_{10}N_2O_2$	54.41	6.53	18.02	54.53	6.54	18.17	3180, 3040, 1685, 1665, 1625	220(11.2) 250(11.9)
IId	253-254	53	$C_7H_{10}N_2O_2$	54.27	6.82	17.94	54.53	6.54	18.17	3180, 3050, 1690, 1675, 1625	219(14.4) 240(12.8)
IIe	299-300	57	$C_8H_{12}N_2O_2$	57.06	6.98	16.56	57.13	7.19	16.66	3180, 3040, 1690, 1670, 1625	218(14.8) 240(13.5)
IIf[5)]	276-277	65	$C_8H_{12}N_2O_2$	56.89	7.08	16.85	57.13	7.19	16.66	3180, 3040, 1710, 1690, 1635	218(15.0) 241(13.4)

a) Decomposition.

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