[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Study of the Cyclization of a Series of ω,ω'-Dicarbethoxydialkylmethylamines through the Acetoacetic Ester Condensation

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There are numerous examples in the literature of the application of an internal acetoacetic ester condensation (the Dieckmann reaction) to the synthesis of cyclic β-keto esters. Dieckmann[1] first used this reaction for the synthesis of five, six and seven membered alicyclic ring structures. In the heterocyclic field use has been made of this reaction in the preparation of both monocyclic and bicyclic systems containing nitrogen as the hetero atom.[2] In this Laboratory the reaction has been applied to the preparation of a number of 1-alkyl-3-carbethoxy-4-piperidones from β,β'-dicarbethoxydiethylalkylamines.[3]

The present paper reports an extension of this work to a series of ω,ω'-dicarbethoxydialkylmethylamines, of the type $C_2H_5OOC(CH_2)_mN(CH_3)(CH_2)_nCOOC_2H_5$, and in which both m and n are varied from 1 to 4. It was the purpose of this work to prepare derivatives of 3-pyrrolidone,[4] the heretofore unknown 3-piperidone, and as many of the larger ring analogs of these cyclic amino ketones as possible.

Sodium ethoxide was used as a condensing agent instead of metallic sodium which had been used in the earlier work.[3] Also three different conditions of reaction, *viz.*, no solvent, benzene as a solvent, and xylene as a solvent, were employed with the various di-esters. It seemed likely that intramolecular rather that intermolecular condensation would be favored by dilution with an inert solvent in those cases where ring formation is more difficult. The alcohol generated in the condensation was removed by distillation as it was formed and its amount determined by direct weighing when no solvent was used, by refractive index of the distillate when benzene was the solvent, and by the phthalic anhydride method[5] in those cases in which xylene was used. By this procedure a more complete reaction was assured and the rate, extent and type of condensation could be roughly determined.

The details of the preparation of the various ω,ω'-dicarbethoxydialkyl-

(1) Dieckmann, *Ber.*, **27**, 102 (1894); *Ann.*, **317**, 27 (1901); *Ber.*, **55**, 2485 (1922).

(2) The following are a few of the pertinent references: (a) Willstätter and Bommer, *Ann.*, **422**, 15 (1921); (b) Ruzicka and others, *Helv. Chim. Acta*, **3**, 816 (1920); **5**, 717 (1922) (c) McElvain and Adams, THIS JOURNAL, **45**, 2738 (1923); (d) Clemo and Ramage, *J. Chem. Soc.*, 441 (1931).

(3) McElvain and others, (a) THIS JOURNAL, **46**, 1721 (1924); (b) **48**, 2179 (1926); (c) **49**, 2862 (1927); (d) **53**, 2692 (1931).

(4) DeMouilipied [*J. Chem. Soc.*, **87**, 442 (1905)] reported the preparation of 1-phenyl-2 or 4-carbethoxy-3-pyrrolidone by a similar condensation. Ruzicka and Seidel [*Helv. Chim. Acta*, **5**, 516 (1922)], however, were unable to isolate a pyrrolidone derivative from an attempted internal condensation of β-carbethoxyethylcarbethoxymethylamine by means of sodium.

(5) Snell and McElvain, THIS JOURNAL, **53**, 2312 (1931).

methylamines are given in the experimental part of the paper. A summary of the reaction conditions and the results of the condensation of these esters with sodium ethoxide are given in Table I. Except in the case of run 7 (see footnote *f*, Table I), the yield of cyclic condensation product given in the sixth column represents the intramolecular condensation product, *i. e.*, the recrystallized hydrochloride of the cyclic amino-β-keto ester which was extractable by ether after the reaction mixture had been acidified with hydrochloric acid and then neutralized with potassium carbonate.[6] The reaction time in the last column of Table I shows the time necessary to obtain the yield of alcohol given in the fifth column.

TABLE I

CONDENSATION OF THE DI-ESTERS, $C_2H_5OOC(CH_2)_mN(CH_3)(CH_2)_nCOOC_2H_5$ BY SODIUM ETHOXIDE

Run	Di-ester *m*	Di-ester *n*	Solvent	Reaction temp., °C.[a]	Yield of C_2H_5OH, %[b]	Yield of cyclic condensation product, %	Unchanged ester recovered, %	Reaction time, hr.
1	2	2	None	120–130	78	62	0	0.33
2	2	2	Benzene	.....	84	71	0	.33
3	3	1	None	110–125	83	85	0	.33
4	2	1	None	120–130	60	36[e]	0	.33
5	2	1	Benzene	.....	85	70[e]	0	.33
6	4	1	Benzene	.....	Traces	0	60	20
7	4	1	Xylene[c]	.....	100	20[f]	0	6
8	1	1	None	120–130	55	0	0	3
9	1	1	Benzene	.....	18	0	30	20
10	4	2	Xylene[c]	.....	20	0	53	20
11	4	2	Xylene[d]	.....	65	0[g]	0	24
12	3	3	None	140–150	50	0	0	2
13	3	3	Benzene	.....	Traces	0	50	40
14	3	3	Xylene[c]	.....	19	0	36	24
15	3	3	Xylene[d]	.....	30	0	18	24
16	4	3	Xylene[c]	.....	3	0	55	20
17	4	3	Xylene[d]	.....	12	0	36	25
18	4	4	Xylene[d]	.....	23	0	21	40

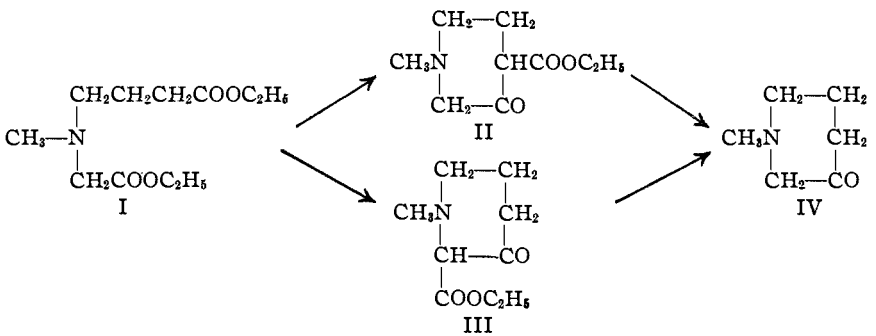
[a] When a solvent was used the reaction temperature was the refluxing temperature of the reaction mixture. [b] Calculated on the basis of an internal acetoacetic ester condensation in which 1 mole of di-ester would produce two moles of alcohol with $NaOC_2H_5$. Obviously less alcohol would be produced if the condensation were intermolecular, *e. g.*, two moles of di-ester would produce two moles of alcohol (50% of that produced by intramolecular condensation) if one molecule of the di-ester condensed with another. [c] In these runs a ratio of 14 g. of di-ester to 200 cc. of xylene was used. [d] A ratio of 14 g. of di-ester to 60 cc. of xylene was used. [e] Extracted with chloroform rather than ether. [f] This value represents the yield of the cyclic amino ketone (1-methyl-aza-1-cycloheptanone-3) hydrochloride rather than the yield of the cyclic amino-β-keto ester. [g] A small amount of ether extractable condensation product was obtained but hydrolysis with 20% hydrochloric acid converted it to δ-N-methylaminovaleric acid hydrochloride. Obviously it was not the expected 8-membered ring compound.

(6) The intermolecular condensation products from two or more molecules of the di-esters were not extractable from the water by ether.

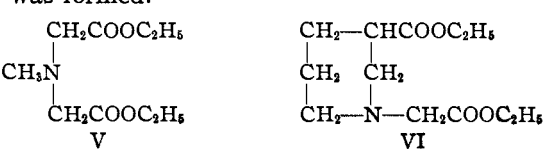
Discussion of the Results

The data obtained in runs 1 and 2 seem to justify two conclusions, (1) that sodium ethoxide is a more efficient condensing agent than metallic sodium for the formation of 1-methyl-3-carbethoxy-4-piperidone (see ref. 3a for results with sodium) and (2) dilution of the reactants with an inert solvent favors the intramolecular condensation.

From run 3 it is seen that γ-carbethoxypropylcarbethoxymethylmethylamine (I) condenses even more readily than the isomeric β,β'-dicarbethoxydiethylmethylamine. Theoretically, the former di-ester could condense to two different 1-methylcarbethoxy-3-piperidones (II and III), both of which, however, would be converted by hydrolysis into 1-methyl-3-piperidone (IV).



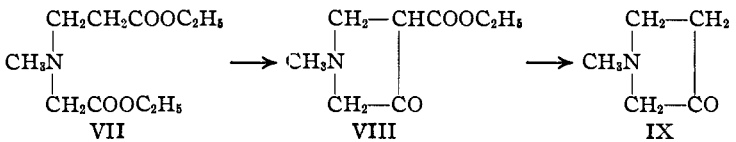
As a matter of fact a good yield of only one condensation product was obtained and it is believed that the structure of this product is given by formula II. This conclusion seems to be justified by the fact that amino di-esters which have the necessary structure (2 hydrogen atoms on an α-carbon atom) for an acetoacetic ester condensation and at the same time have an amino group attached to this α-carbon atom react very slowly, if at all, with sodium ethoxide or sodium in condensations involving this particular α-carbon atom. Runs 8 and 9 with dicarbethoxydimethylmethylamine (V) illustrate this behavior. Also it has been found[7] that ethyl (3-carbethoxypiperidino)-acetate (VI) was recovered for the most part unchanged after refluxing with either sodium ethoxide or metallic sodium in benzene, toluene, xylene or cymene solutions. Obviously the formation of structure (III) would involve condensation through an α-carbon atom carrying an amino substituent. Since the condensation took place so readily (85% in twenty minutes) it seems likely that the alternative structure (II) was formed.



(7) McElvain and Adams, THIS JOURNAL, 45, 2746 (1923).

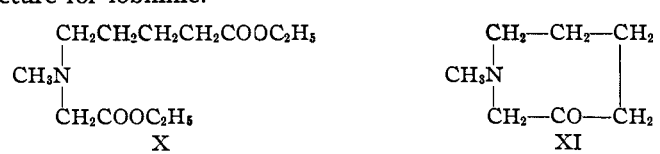
The keto ester (II) was hydrolyzed readily into 1-methyl-3-piperidone (IV). These compounds (II and IV) are the first examples of a 3-piperidone to be prepared.[8] The 1-methyl-3-piperidone differs quite markedly from the isomeric 4-piperidone in that it is extremely easily oxidized, even by air, and reduces both ammoniacal silver nitrate and Fehling's solution immediately in the cold. In fact it shows the characteristic properties of an α-amino ketone.[9]

For the reason given above it is believed that β-carbethoxyethylcarbethoxymethylmethylamine VII (runs 4 and 5) condensed to 1-methyl-4-carbethoxy-3-pyrrolidone VIII, since only a single compound was obtained from the reaction. This latter compound was readily hydrolyzed to the corresponding pyrrolidone (IX). This compound, on account of its α-amino ketone structure, showed the same susceptibility to oxidation as the 1-methyl-3-piperidone.



It should be noted that in this case dilution of the reactants with an inert solvent (run 5) was decidedly favorable for intramolecular condensation.

With δ-carbethoxybutylcarbethoxymethylmethylamine (X) the time for the formation of a substantial yield of alcohol begins to increase. The hydrochloride of the condensation product which was isolated directly from the reaction could not be caused to crystallize. This may have been due to the presence of both of the possible isomeric β-keto esters, since the conditions and time of reaction were perhaps sufficiently strenuous and prolonged in run 7 to have caused some condensation on the α-carbon atom attached to the amino group. Since both of these isomeric β-keto esters would be converted to the same cyclic ketone, the reaction product was hydrolyzed and the hydrochloride of 1-methyl-aza-1-cycloheptanone-3 (XI) isolated. This seven-membered heterocyclic ring structure is of interest in connection with the recent synthesis of a bicyclic analog, N-methyl-homogranatonine,[10] and the suggested seven-membered nitrogen ring structure for lobinine.[11]



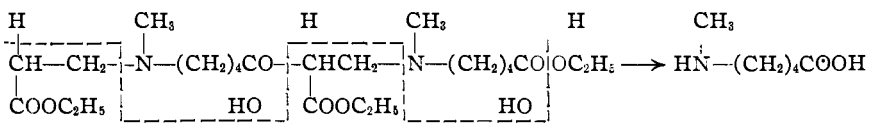
(8) Clemo and Ramage[2d] recently reported the preparation of a bicyclic analog of 3-piperidone, ethyl 1-keto-octahydropyridocoline-2-carboxylate.

(9) *Cf.* Beilstein, "Handbuch der organ. Chem.," 1922, Vol. IV, pp. 314, 316.

(10) Blount and Robinson, *J. Chem. Soc.*, 1429 (1932).

(11) Wieland, Ishimasa and Koschara, *Ann.*, **491**, 14 (1931).

The behavior of dicarbethoxydimethylmethylamine (runs 8 and 9) has been referred to above. β-Carbethoxyethyl-δ-carbethoxybutylmethylamine which should have produced an eight-membered ring showed very little reaction in dilute xylene solution (run 10) after twenty hours. However, in more concentrated xylene solution (run 11) the higher yield of alcohol suggests an intermolecular condensation. The ether extraction for the intramolecular condensation product yielded a small amount (about 3% yield calculated as the expected cyclic β-keto ester) of material which gave a definite coloration with ferric chloride and which was converted by hydrolysis with 20% hydrochloric acid into the hydrochloride of δ-N-methylaminovaleric acid (see footnote *g*, Table I). This latter product undoubtedly resulted from the deamination[12] during hydrolysis of a small amount of an intermolecular condensation product which had been extracted by the ether. To illustrate with the simplest example



It is seen from Table I that none of the di-esters higher than δ-carbethoxybutylcarbethoxymethylmethylamine ($m = 4$, $n = 1$) give isolable quantities of intramolecular condensation products. It should be pointed out in this connection that Littmann and Marvel[13] obtained an eight-membered cyclic quaternary salt from ω-bromoheptyldimethylamine. However, while ε-aminocaproic acid is partially converted to the seven-membered cyclic lactam structure, ζ-aminoheptanoic acid gives none of the eight-membered cyclic lactam, but only open-chain polyamides.[14]

Experimental

Materials Used

ω-Halogen Esters.—Ethyl chloroacetate was prepared by esterification of chloroacetic acid. Ethyl β-bromopropionate was prepared from ethylene cyanohydrin.[15] γ-Bromobutyric acid was prepared by the hydrolysis of γ-bromobutyronitrile[16] with 48% hydrobromic acid and esterified by the procedure described for ethyl β-bromopropionate.[15] The yield of ethyl γ-bromobutyrate from the bromonitrile was 72% of the theoretical. This ester has not been described previously in the literature. It boils at 104–105° (28 mm.); n_D^{25} 1.4539; d_{25}^{25} 1.3531; M_D calcd., 39.33, found, 39.14. *Anal.* Calcd. for $C_6H_{11}O_2Br$: Br, 41.00. Found: Br, 41.03. Ethyl δ-bromovalerate was prepared from δ-bromovaleric acid[17] by the esterification procedure[15] used above. This ester has been prepared previously.[17]

ω-(N-Methylamino) Esters.—Ethyl N-methylaminoacetate (sarcosine ester)

(12) *Cf.* Thomas and McElvain. THIS JOURNAL, **54**, 3295 (1932).
(13) Littmann and Marvel. *ibid.*, **52**, 287 (1930).
(14) Carothers and Berchet, *ibid.*, **52**, 5289 (1930).
(15) "Organic Syntheses," 1923, Vol. III, p. 51.
(16) Derick and Hess, THIS JOURNAL, **40**, 547 (1918).
(17) Merchant, Wickert and Marvel, *ibid.*, **49**, 1828 (1927).

hydrochloride was prepared by the alcoholysis of methylaminoacetonitrile[18] by the procedure described by Staudt.[19] The ethyl N-methylaminoacetate hydrochloride after recrystallization from chloroform melted at 126–127°.[20] The free amino ester, ethyl N-methylaminoacetate, was liberated from its hydrochloride just before it was used by the following method. A suspension of the hydrochloride in dry ether was treated with dry ammonia gas until all of the particles of the hydrochloride appeared to be replaced by the very finely divided precipitate of ammonium chloride. This precipitate was filtered off, suspended in a fresh portion of ether, and again treated with ammonia. After filtration these ethereal solutions were combined and, after removal of the ether, the amino ester was distilled. It boiled at 59–60° (25 mm.) and the recovery from the hydrochloride amounted to 90% of the theoretical.

Ethyl β-N-methylaminopropionate was prepared by a method previously described.[21] This amino ester could be converted into a crystalline hydrochloride, m. p. 59–60°.

Anal. Calcd. for $C_6H_{14}O_2NCl$: Cl, 21.16. Found: 20.99.

Ethyl δ-N-methyl aminovalerate was prepared in the following manner. 1-Methyl-2-pyridone[22] was hydrogenated over nickel to 1-methyl-2-piperidone.[23] The yield of product boiling at 97–98° (11 mm.) was practically quantitative. This piperidone gives a hygroscopic hydrochloride, m. p. 104–105°.[24] To 57 g. of this piperidone was added a solution of 40 g. of sodium hydroxide in 100 cc. of water and this solution refluxed for one hour. After cooling 150 cc. of concentrated hydrochloric acid was added and the solution evaporated to dryness under diminished pressure. The residue was extracted with 150 cc. of boiling absolute alcohol and the insoluble sodium chloride removed by filtration. To the alcoholic solution was added 300 cc. of absolute alcohol containing 10% dry hydrogen chloride. This solution was refluxed for eight hours and then evaporated to dryness under diminished pressure. To complete the esterification the residue was refluxed for an additional eight hours with another 400-cc. portion of absolute alcohol containing 6% of dry hydrogen chloride. On evaporation of this solution under diminished pressure a residue of ethyl δ-N-methylaminovalerate hydrochloride remained which after recrystallization from ethyl acetate melted at 108–109°.

Anal. Calcd. for $C_8H_{18}O_2NCl$: Cl, 18.13. Found: Cl, 18.07.

The free amino ester was liberated from this hydrochloride in the same manner as described above for ethyl-N-methylaminoacetate. The ethereal solution of the free amino ester was freed from the ether by distillation and the higher boiling residue used directly in the subsequent experiments. Distillation of this residue of free amino ester caused a considerable amount of it to be converted into the original lactam, 1-methyl-2-piperidone. Also, standing at room temperature caused this amino ester to change into the lactam and alcohol. For this reason no analyses or determinations of physical properties were made.

ω,ω′-Dicarbethoxydialkylmethylamines.—β,β′-Dicarbethoxydiethylmethylamine was prepared from ethyl β-bromopropionate and methylamine by a procedure pre-

(18) Biltz and Slotta, *J. prakt. Chem.*, [2] **113**, 252 (1926).

(19) Staudt, *Z. physiol. Chem.*, **146**, 286 (1925).

(20) *Cf.* Sigmund and Liedl, *ibid.*, **202**, 268 (1931).

(21) McElvain, THIS JOURNAL, **46**, 1726 (1924).

(22) Decker, *J. prakt. Chem.*, [2] **47**, 28, 222 (1893); *ibid.*, [2] **84**, 219, 432 (1911). This procedure involves the oxidation of pyridine methosulfate with potassium ferricyanide. It was found advantageous to modify this procedure at two points. First, the order of addition of reactants was reversed, *i. e.*, the ferricyanide and alkali solutions were slowly added to the solution of the pyridine methosulfate. Second, amyl alcohol was used to extract the pyridone instead of benzene since it was found that benzene failed to dissolve the pyridone hydrate, a form in which considerable of the pyridone is present.

(23) Covert, Connor and Adkins, THIS JOURNAL, **54**, 1658, 1661 (1932).

(24) *Cf.* Rath, *Ann.*, **489**, 113 (1931).

viously described.[25] γ,γ'-Dicarbethoxydipropylmethylamine was likewise prepared from methylamine and ethyl γ-bromobutyrate, but it was necessary to use the following procedure on account of the lower reactivity[26] of this bromo ester. A solution of 60 g. (0.3 mole) of ethyl γ-bromobutyrate in 50 cc. of absolute alcohol was refluxed gently in a 1-liter flask fitted with a reflux condenser and a dropping funnel. To this boiling solution a solution of 16 g. (0.5 mole) of methylamine in 150 cc. of absolute alcohol was added slowly over a period of four hours. The solution was then refluxed for an additional four hours. Then about 100 cc. of alcohol was distilled out and on cooling a crop of methylamine hydrobromide crystals which separated was filtered off. The remaining alcohol was removed under diminished pressure. The residue was treated with 50-cc. of water and sufficient hydrochloric acid to give a distinct acid reaction to Congo red. The unreacted bromo ester was then extracted with ether, after which the aqueous solution was neutralized with potassium carbonate and the γ,γ'-dicarbethoxydipropylmethylamine extracted with petroleum ether. After removal of this solvent under diminished pressure, 6 g. of the tertiary amino ester boiling at 162–166° (14 mm.) was obtained. The aqueous layer was further extracted with chloroform and this extract distilled. After removal of the chloroform, 6 g. of 1-methyl-2-pyrrolidone,[27] b. p. 82–87° (14 mm.) and 5 g. of a fraction boiling at 115–170° (14 mm.) were obtained This latter fraction was dissolved in petroleum ether and shaken with several portions of water to remove any of the pyrrolidone. This petroleum ether extract on distillation yielded an additional 2 g. of γ,γ'-dicarbethoxydipropylmethylamine, b. p. 162–166° (14 mm.) The total yield was therefore 8 g. or 20% of the theoretical.

The remainder of the ω,ω'-dicarbethoxydialkylmethylamines were prepared by the interaction of 1 mole of an ω-halogen ester and 2 moles of an ω-N-methylamino ester (see Table II). The reactants were mixed and allowed to stand from four to twenty-four hours at room temperature, after which time the reaction mixture was diluted with ether. The secondary amino ester hydrohalide which precipitated was separated from the ethereal solution and then the latter was distilled. In those cases when ethyl δ-N-methylaminovalerate was used a considerable amount of 1-methyl-2-piperidone was formed in the reaction.

All of these tertiary amino esters before use were subjected to the following general method of purification. After fractionation at the time they were prepared, they were allowed to stand in stoppered bottles for a month or more. During this time any halogen ester which might be present reacted with the tertiary amine and any unchanged secondary amino ester reacted with itself to form a lactam, a diketopiperazine, or an open chain condensation product. The product was then dissolved in ten times its volume of petroleum ether and shaken with several small portions of water in order to remove any of these secondary reaction products, all of which are preferentially dissolved in the water layer. The petroleum ether solution was then dried over anhydrous sodium sulfate and, after removal of the solvent, the product was distilled. There was very little loss resulting from this purification process.

Table II gives the data concerning the preparation, properties and analyses of these tertiary amino esters.

The Condensation of ω,ω'-Dicarbethoxydialkylmethylamines by Sodium Ethoxide. I. Without a Solvent.—One mole of the di-ester and 1 mole of sodium ethoxide were mixed in a distilling flask fitted with a mercury-sealed stirrer and a condenser set for downward distillation. A tared receiver, protected by a soda lime tube, was attached to the condenser. With the stirrer in operation the flask was immersed in an oil-bath and

(25) McElvain, THIS JOURNAL, **46**, 1724 (1924); Bolyard, University of Wisconsin, Ph.D. Thesis, 1928.

(26) *Cf.* Wohlgemuth, *Ann. Chim.*, **2**, 314 (1914).

(27) Tafel and Wassmuth, *Ber.*, **40**, 2839 (1907); Gansser, *Z. physiol. Chem.*, **61**, 59 (1909).

heated to the temperature indicated in Table I. The reaction was continued until no more alcohol distilled out.

TABLE II

ω,ω'-DICARBETHOXYDIALKYLMETHYLAMINES, $C_2H_5OOC(CH_2)_mN(CH_3)(CH_2)_n$-$COOC_2H_5$

$$\begin{array}{c} (CH_2)_mR^a \\ | \\ H\text{—}N\text{—}CH_3 \end{array}$$

m	n	Formula	used[d] m is	Yield,[e] %	B. p., °C. (mm.)	d_{25}^{25}	n_D^{25}	M_D Calcd.	M_D Found	Analyses, N, % Calcd.	Found
2	2[b]	$C_{11}H_{21}O_4N$	.	70	134–135 (10)	....	....	...	...	..	..
3	3[c]	$C_{12}H_{23}O_4N$	.	20	159–160 (9)	0.9913	1.4407	69.48	69.19	5.40	5.37
1	1	$C_9H_{17}O_4N$	1	75	114–115 (11)	1.0485	1.4328	51.01	50.48	6.89	6.91
1	2	$C_{10}H_{19}O_4N$	1	85	124–125 (10)	1.0287	1.4350	55.63	55.13	6.45	6.48
1	3	$C_{11}H_{21}O_4N$	1	80	134–135 (10)	1.0145	1.4367	60.25	59.85	6.05	5.90
4	1	$C_{12}H_{23}O_4N$	4	73	146–147 (9)	1.0032	1.4393	64.86	64.78	5.71	5.64
4	2	$C_{13}H_{25}O_4N$	4	54	159–160 (9)	0.9914	1.4410	69.48	69.26	5.40	5.38
4	3	$C_{14}H_{27}O_4N$	4	58	166–167 (9)	.9814	1.4420	74.10	73.89	5.12	5.11
4	4	$C_{15}H_{29}O_4N$	4	55	177–178 (9)	.9741	1.4438	78.72	78.55	4.87	4.81

[a] R = $COOC_2H_5$. [b] This compound has been described previously.[25] [c] This ester was prepared from methylamine and $Br(CH_2)_3COOC_2H_5$. [d] The halogen ester, $X(CH_2)_nCOOC_2H_5$ reacts with this secondary amino ester in the cases where the latter is used. [e] Of tertiary amino ester and based on amount of ω-halogen ester used in the reaction.

II. **Benzene** as a Solvent.—A three-necked flask of suitable size was fitted with a mercury seal stirrer and a Vigreaux fractionating column surrounded by a jacket. By filling this jacket with water the column could be used as a reflux condenser. A thermometer was inserted in the head of the column and the side arm attached to a condenser set for downward distillation. A solution of 30–40 g. of the di-ester in 250 cc. of benzene and the theoretical amount of sodium ethoxide were then added through the third neck of the reaction flask. The flask was then heated in an oil-bath with the jacket of the column empty until the azeotropic mixture of alcohol and benzene distilled out and the thermometer reached the boiling point of benzene. Then water was circulated through the jacket for a few minutes, after which the water again was run out and the distillation carried out as before. This process was repeated until the distillate showed the refractive index of pure benzene. The amount of alcohol in the distillate was determined from its refractive index. Most of the benzene was then removed from the residue in the reaction flask by distillation and about 120 cc. of water added, and the amino-β-keto ester isolated as the hydrochloride by the procedure previously described.[3a]

III. **Xylene** as a Solvent.—The same apparatus was used as when benzene was the solvent except that the column was not surrounded by a jacket. The ratio of reactant to solvent is given in Table I, footnotes *c* and *d*. The reaction flask was heated in an oil-bath sufficiently to cause gentle refluxing from the column. Periodically the temperature of the bath was raised and the mixture of alcohol and xylene distilled out until the thermometer registered the boiling point of xylene. When no more alcohol came over the remaining xylene was removed under diminished pressure from the reaction mixture. The seven membered cyclic amino-β-keto ester was found to differ from its 5 and 6 membered ring analogs in that it was extractable by ether from an aqueous solution of its sodium derivative. Consequently the extraction for the cyclic β-keto ester was made after the reaction mixture had been treated with water. When such an extraction was carried out until the ether extracts showed no coloration with ferric chloride, treatment of the remaining aqueous solution by the usual isolation procedure[3a] yielded no additional condensation product. The alcohol in the distillate was determined by

the phthalic anhydride method.[5] The properties and analyses of the new cyclic amino-β-keto ester hydrochlorides isolated in the present work are given in Table III.

TABLE III

CYCLIC AMINO-β-KETO ESTER HYDROCHLORIDES

Compound, hydrochloride	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
1-Methyl-4-carbethoxy-3-piperidone	$C_9H_{16}O_3NCl$	171–173 (decomp.)	48.82	7.27	16.00	48.51	7.21	15.98
1-Methyl-4-carbethoxy-3-pyrrolidone	$C_8H_{14}O_3NCl$	132–133	46.24	6.80	17.09	45.93	6.93	17.05

The β-keto esters of Table III as well as the uncrystallizable β-keto ester resulting from the intramolecular condensation of δ-carbethoxybutylcarbethoxymethylmethylamine were hydrolyzed by refluxing in dilute hydrochloric acid until the solution showed no coloration with ferric chloride. Evaporation of this acid solution left the hydrochloride of the corresponding ketone, which was recrystallized from dry acetone. In certain cases the free bases were prepared from the hydrochlorides. These compounds are summarized in Table IV. For comparison some of the properties of the corresponding 2-pyrrolidone and the 2- and 4-piperidones are included in this table.

TABLE IV

CYCLIC AMINO KETONES, $CH_3N\langle^{(CH_2)_m}_{(CH_2)_n}\rangle CO$, AND THEIR HYDROCHLORIDES

m	n	B. p., °C. (mm.)	d_{25}^{25}	n_D^{25}	M_D Calcd.	M_D Found	Analyses, N, % Calcd.	Found	Hydrochloride, m. p., °C.	Hydrochloride analyses, Cl, % Calcd.	Found
2	1	46–47 (18)	0.9675	1.4431	27.04	27.23	14.13	14.06	62– 63	26.17	24.50[a]
3	0[b]	84–85 (14)	1.0260	1.4666	27.04	26.86	...	...	79– 81	26.17	25.89
2	2[c]	56–58 (11)	0.9725	1.4580	31.66	31.83	12.38	12.31	94– 95[c]	...	...
3	1	63–64 (13)	.9684	1.4559	31.66	31.64	12.38	12.40	110–111	23.71	23.52
4	0	97–98 (11)[d]	1.0293	1.4801	31.66	31.31	...	...	104–105[e]	...	...
4	1	... ..	....	....	...	...	...	...	195–196	21.68	21.46[f]

[a] Low analyses in this case are probably due to solvent of crystallization, *cf.* Bolyard and McElvain, THIS JOURNAL, 51, 924 (1929). [b] *Cf.* Ref. 27. [c] The hydrochloride of this ketone has been described (see ref. in footnote *a*), but the free ketone was not isolated. [d] *Cf.* Ruzicka, *Helv. Chim. Acta*, 4, 474 (1921). [e] *Cf.* Ref. 24. [f] Additional *Anal.* Calcd.: C, 51.34; H, 8.63. Found: C, 51.28; H, 8.75.

Summary

A series of ω,ω'-dicarbethoxydialkylmethylamines, $C_2H_5OOC(CH_2)_m$-$N(CH_3)(CH_2)_nCOOC_2H_5$, in which both m and n are varied from 1 to 4, have been prepared and their cyclization through an internal acetoacetic ester condensation under a variety of conditions has been studied.

Derivatives of 3-pyrrolidone, 3- and 4-piperidone, and aza-1-cycloheptanone-3 have resulted from the intramolecular condensation of certain of these di-esters. With the other di-esters of the series the condensation, as judged by the amount of alcohol given off, was quite slow and incomplete and went to give intermolecular condensation products.

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