Five- and Six-Membered Ring Formation by the Competitive Dieckmann Cyclization of an Amino Triester[1]

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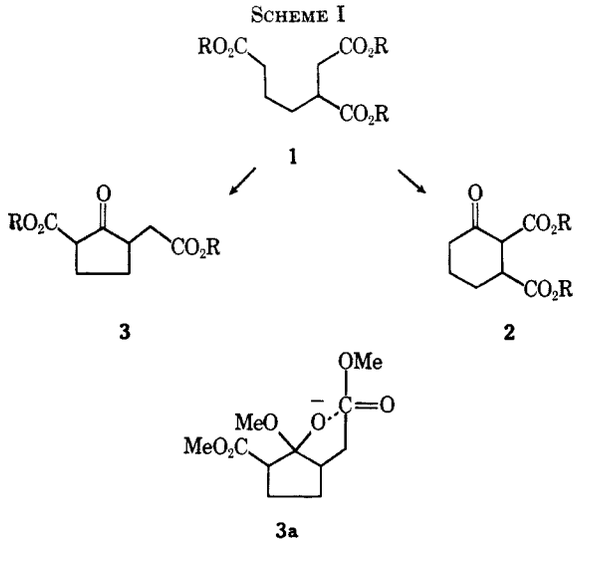
The cyclization of diethyl N-(2-carbethoxyethyl)-N-methylaspartate (**6**), using sodium hydride in benzene, sodium in toluene, or sodium ethoxide in ethanol, gave only the six-membered ring product, 1-methyl-2,3-dicarbethoxy-4-piperidone (**8**). Under nonreversible conditions (potassium *t*-butoxide in toluene at −20°) 1-methyl-2-carbethoxymethyl-4-carbethoxy-3-pyrrolidinone (**10**) was the primary product. These results are discussed in the light of the data obtained from the literature on the cyclization of triethyl 3-carboxypimelate (**1**).

The problem of direction of ring closure in the cyclization of polycarboxylic esters by means of the Dieckmann condensation has long been a vexing one. In those cyclizations in which there is a competition between the formation of a cyclopentanone or a cyclohexanone and a ring of another size, the results were not unusual with only the five- or six-membered ring formation observed.[3] However, in the work involving competitive cyclization between five- and six-membered rings a certain amount of confusion exists. The cyclization of trialkyl 3-carboxypimelate (**1**) with sodium or sodium hydride in benzene gives the dicarboxycyclohexanone, **2**,[4,5] while the use of sodium ethoxide in ethanol as the condensing agent results in the formation of the substituted cyclopentanone, **3**[5,6] (Scheme I).

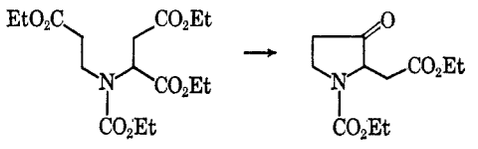
SCHEME I



These results can be interpreted as being the result of kinetic and thermodynamic control of the reaction with the extraction of the most acidic proton in nonprotic media being responsible for the formation of the six-membered ring while equilibration in protic media would lead to the more stable cyclopentanone. This interpretation is supported by the direction of ring closure of a highly substituted triester[7] as well as the closure of unsymmetrical hetero diesters.[8,9]

This postulate, however, does not agree with the results obtained on competitive cyclization of a mixture of equal amounts of dimethyl adipate and dimethyl pimelate using 1 equiv of base. Using sodium methoxide in methanol as the condensing agent it was found that the cyclopentanone was the more readily formed but that the equilibrium mixture strongly favored the cyclohexanone.[5] The fact that **2** and **3** can be interconverted[5,10] by the proper choice of conditions also sheds some doubt on this proposal and led to the proposal that, in the cyclization of **1** in hydroxylic solvents, internal solvation of the five-membered-ring transition state, **3a**, by the ester side chain accounts for the preferred formation of **3**.[5] A dependency on solvent has also been reported by Carrick and Fry[11] in their determination of the C^{14} isotope effect in the Dieckmann cyclization of diethyl phenylenediacetate, with a value of 1.6 ± 0.5% observed with sodium in toluene and 5.6 ± 0.7% found with sodium ethoxide in ethanol.

Only one report could be found concerning the competition between the formation of five- and six-membered rings containing a heteroatom. Clark-Lewis and Mortimer[12] state that only the pyrrolidinone **5** was formed on cyclization of the triester **4** with sodium in benzene followed by decarboxylation. This is in contradiction to what has been found on cyclization of **1** in which the six-membered ring formation is favored under these conditions.[4,5]



It thus became apparent that more work was necessary in order to ascertain whether the cyclizations of amino triesters followed the generalizations observed in the carbocyclic series or whether the results re-

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(2) Taken in part from the theses submitted by Z. S. Z. (1966) and D. H. M. (1965) to Seton Hall University in partial fulfillment of the requirements for the M.S. degree.

(3) (a) F. W. Kay and W. H. Perkin, *J. Chem. Soc.*, **89**, 1647 (1906); (b) H. T. Openshaw and R. Robinson, *ibid.*, 912 (1946); (c) W. S. Johnson, R. G. Christiansen, and R. E. Ireland, *J. Am. Chem. Soc.*, **79**, 1995 (1957).

(4) (a) M. E. Dobson, J. Ferns, and W. H. Perkin, *J. Chem. Soc.*, **95**, 2010 (1909); (b) K. Sen and P. Bagchi. *Sci. Cult.* (Calcutta), **19**, 312 (1953).

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(7) R. B. Turner, K. H. Ganshirt, P. E. Shaw, and J. D. Tauber, *J. Am. Chem. Soc.*, **88**, 1776 (1966).

(8) (a) R. B. Woodward and R. M. Eastman, *ibid.*, **68**, 2229 (1946); (b) B. R. Baker, M. V. Querry, S. R. Safir, and S. Bernstein, *J. Org. Chem.*, **12**, 138 (1947); (c) G. B. Brown, M. D. Armstrong, A. W. Moyer, W. P. Anslow, Jr., B. R. Baker, M. V. Querry, S. Bernstein, and S. R. Safir, *ibid.*, **12**, 160 (1947).

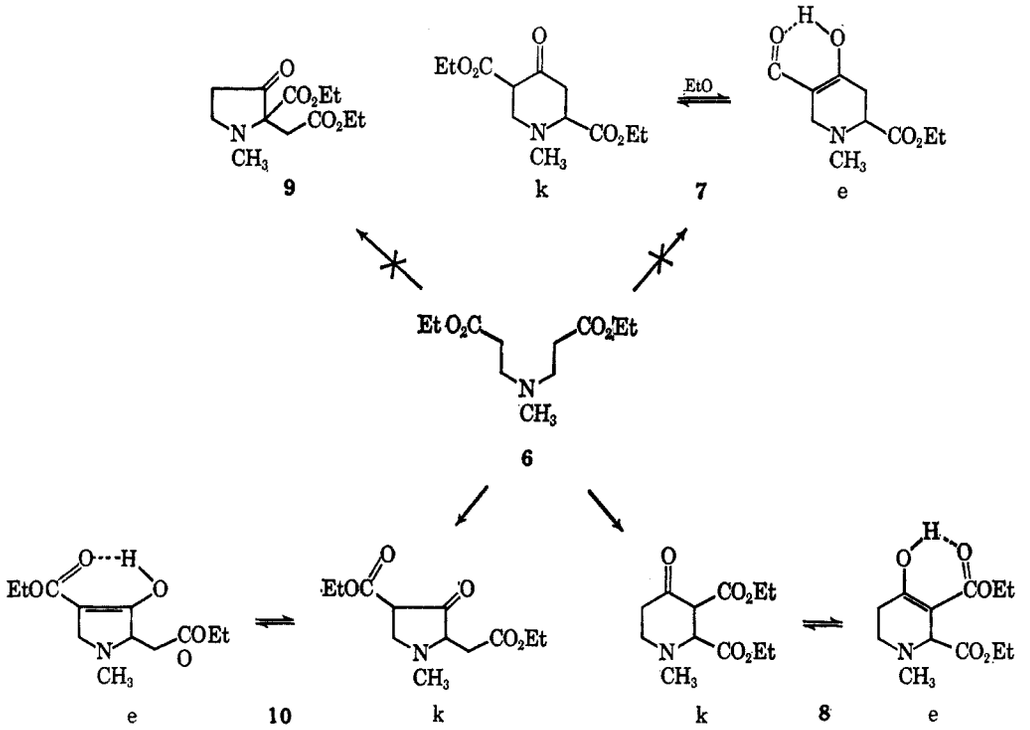
(9) J. Blake, C. D. Willson, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 5293 (1964).

(10) D. K. Banerjee, J. Dutta, and G. Bagavant, *Proc. Indian Acad. Sci. Sect B*, **46**, 80 (1957).

(11) W. L. Carrick and A. Fry, *J. Am. Chem. Soc.*, **77**, 4381 (1955).

(12) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1961).

SCHEME II



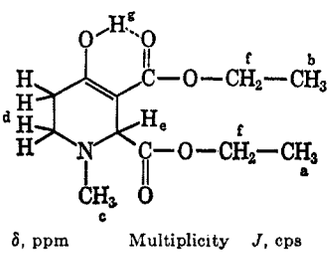
ported by Clark-Lewis and Mortimer[12] were typical for this type of compound. The compound selected for this study, diethyl N-(2-carbethoxyethyl)-N-methylaspartate (**6**), was readily prepared by the reaction of diethyl N-methyl aspartate with ethyl acrylate. It was found that optimum yields of **6** were obtained when the reactants were refluxed, without solvent, in the presence of a small amount of acetic acid for 24 hr. Shorter reaction times as well as the omission of the acetic acid resulted in a much lower yield of **6** while longer reaction times favored the formation of 2,2-dicarbethoxydiethylmethylamine, apparently by reverse Michael and reaction of methylamine with ethyl acrylate.

The various possible products which could be obtained by cyclization of **6** are shown in Scheme II. By analogy with the carbocyclic reaction pathway, the dicarbethoxypiperidone (**8**) would be expected from condensation of **6** with sodium hydride in benzene. On the other hand, if the results of Clark-Lewis and Mortimer[12] were typical, a pyrrolidinone (**9** or **10**) would be formed. When the triester was cyclized under these conditions it was found by vpc analysis that, after a 30-min reflux, all of the starting material had reacted and that the product was composed predominantly of two components, A (65–75%) and B (25–35%). It was also shown that the product ratio changed in favor of B on prolonged heating of the reaction mixture as well as on letting the crude product stand at room temperature for extended periods of time. Attempted distillation of this mixture was unsuccessful with only intractible tar being formed in the distillation pot. Isolation of the two components was achieved, however, by conversion of the materials to their hydrogen halide or perchlorate salts.

Component A was isolated as a solid salt analyzing as $C_{12}H_{19}O_5N \cdot HX$ from which the free base could be obtained in 99% purity (vpc) by partitioning between aqueous sodium bicarbonate and ether at 0–5°. The product so obtained gave a positive ferric chloride test and had an infrared spectrum typical of a highly enolic β-keto ester with bands at 1701 (unchelated ester) 1661 (chelated enol) and 1629 cm^{-1} (enol double bond). The absence of the typical pyrrolidinone band at 1770 cm^{-1} [12,13] and the enolic character of the product conclusively eliminated **9** from consideration. However, the compound may have been **10** since this band is not necessarily present in the infrared spectra of highly enolic 4-carbethoxy-3-pyrrolidinones.[8]

That the product was actually **8e** was established by analysis of its nmr spectrum. The spectral assignments are given in Table I. A primary factor in assigning this structure is the presence of a one-proton singlet at δ 4.05 for the C_2 proton in **8e**. Both **7e** and **10e** would be expected to have a two-proton singlet at δ 2.5–2.7 for the C_6 and C_5 protons, respectively,[14] a peak which is absent in the observed spectrum.

TABLE I

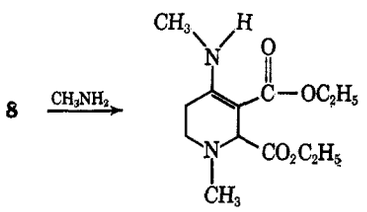


Proton	δ, ppm	Multiplicity	J, cps	Integrated area
a	1.24	3	7.1	3
b	1.28	3	7.1	3
c	2.43	1	...	3
d	2.16–2.38	m	...	4.1–4.2
e	4.05	1	...	1
f	4.20	4	7.1	4
g	12.05	1	...	0.8–0.9

(13) I. K. Morita, A. V. Robertson, and B. Witkop, *J. Am. Chem. Soc.*, **85**, 2824 (1963).

(14) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p 84.

The second component (B) of the reaction mixture was separated from the mixture of hydrogen chloride salts as a viscous oil which resisted crystallization. On liberation the free base was obtained about 95% pure (vpc). The infrared spectrum of this material had bands at 3289, 1730, 1650, and 1600 cm^{-1}. Since these last two bands are similar to those observed for vinylogous amides (N—C=C—C=O),[15,16] it was felt that this material was the vinylogous urethan, **11**. This assumption was found to be correct when it was shown that B was formed on treatment of **8** with methylamine. The nmr spectrum also agreed with this assignment (see the Experimental Section). The methylamine responsible for the formation of **11** in the cyclization reaction undoubtedly arises from the reverse Michael reaction of either **6** or **8**.



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It was interesting, then, to find that at least when sodium hydride in benzene was used the results from the cyclization of **6** paralleled those obtained from cyclization of **1** with one distinction. Cyclization of **1** under these conditions gave an 80:20 mixture of the six- and five-membered ring compounds[5] while we were unable to detect (vpc) the presence of an appreciable amount of anything other than **10** and its enamine **11**. Repetition of the cyclization of **6** using sodium in toluene gave the same results as found using sodium hydride.

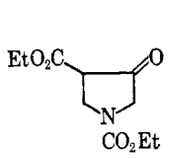
Deviation from the carbocyclic series was observed on cyclization of **6** using sodium ethoxide in ethanol. Under these conditions five-membered ring formation was expected.[5,6] However, only starting material and **8** were observed (vpc) with the yield of **8** being much lower than that obtained with sodium hydride even when longer reaction times were used.

Attention was then directed toward an attempt to prepare either **9** or **10** under irreversible conditions.[9] Condensation of **6** was carried out using potassium *t*-butoxide in toluene at −25°. After 30 min the reaction mixture was neutralized by the addition of 1 equiv of *p*-toluenesulfonic acid. The potassium sulfonate salt which precipitated on addition of ether was filtered and the filtrate was concentrated giving a crude product mixture in about 90% yield. Vpc analysis of this mixture showed the presence of a small amount of starting material and the presence of two major components in 58 and 28% yield, respectively. The second component was chromatographically indistinguishable from **8**.

The major component was isolated from the mixture by fractional crystallization of the hydrogen chloride salt. Elemental analysis of the salt showed it to be isomeric with **8**·HCl. This salt gave a positive ferric chloride test. Liberation of the free base gave a product of about 95% purity (vpc) which had adsorption bands in the infrared at 1701 (ester) and 1770 cm^{-1} (pyrrolidinone).[12,13] This, plus the enolic character of the material, led to the assignment of structure **10** to this material. The nmr spectrum is consistent with this assignment (see the Experimental Section). The absence of any chelated ester or enolic double bond adsorption in the infrared indicates that, in contrast to **8**, this five-membered cyclic β-keto ester (**10**) exists almost exclusively in the keto form. These data are in agreement with the results obtained for the keto ⇌ enol equilibria of the five- and six-membered carbocyclic β-keto esters[17] but do not coincide with the report that **12** showed the strong enolic bands.[9] It should be noted, however, that the hydrochloride of **10** did show the chelated ester and enol double bond absorptions in the infrared.[18]

The competitive cyclization of the amino triester (**6**) therefore, follows to some extent the results observed with the aliphatic triester **1**. The obtaining of 2,3-dicarbethoxy-4-piperidone (**8**) using sodium hydride in benzene was as expected, but the lack of five-membered ring formation with sodium ethoxide in ethanol was somewhat surprising. The obtaining of the pyrrolodinone (**10**) only with potassium *t*-butoxide under established irreversible conditions[9] negates the suggestion[5] that cyclohexanone formation in sodium hydride–benzene was a result of the extraction of the most acidic proton (irreversible conditions). If this were the case, it would be expected to obtain the same product from both sodium hydride and potassium *t*-butoxide. This was not what was found.

An alternative proposal can, however, be made. It is possible that, in nonpolar media under conditions which would permit the equilibration of the anion, six-membered ring formation is favored because of an intramolecular stabilization of the transition state by the neighboring carbonyl oxygen as in **13**. Such stabilization would be expected to be more important in nonpolar media than in polar solvents, but, in the sodium ethoxide–ethanol reaction, the most stable isomer is the one formed. In the heterocyclic series, the same compound is formed under both conditions; so little can be said about the relative stabilities. In the carbocyclic series, however, it would be expected that the cyclopentanone would be more stable,[19] but this, again, is in contrast to the results obtained on competitive cyclization of diethyl adipate and diethylpimelate.[5]



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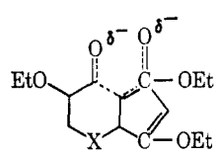

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It is evident, then, that no single explanation can be put forth for the results found in these reactions. It is almost certainly true that both intramolecular and intermolecular solvation as well as proton acidities and anion stabilities all play an important role. Work

(15) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959).
(16) G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).
(17) S. J. Rhoads, *ibid.*, **31**, 171 (1966).
(18) The factors involved in the enol ⇌ keto equilibrium of five- and six-membered heterocyclic β-keto esters will be the subject of a future publication.
(19) H. C. Brown, J. H. Brewster, and H. Schecter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

has recently been initiated in an attempt to gain an understanding of the relative importance of each of these factors in determining the outcome of this type of cyclization.

Experimental Section[20]

Diethyl N-Methylaspartate.—The procedure used was a modification of that described by Lynch.[21] A solution of 62 g (2 moles) of methylamine in absolute alcohol was added in portions at 0–5° to 344 g (2 moles) of diethyl maleate with occasional stirring and ice-bath cooling in order to maintain the exothermic reaction below 10°. After addition was complete the flask was stoppered and kept in the cooling bath for 30 min and then allowed to stand at room temperature for 48 hr. The ethanol was removed under reduced pressure with gentle warming and the residual oil was purified by distillation: 352 g (86.5%), bp 94–97° (0.45 mm), n^{26}D 1.43296.

Diethyl N-(2-Carbethoxyethyl)-N-methylaspartate (6).—To a reaction flask containing 101.6 g of diethyl N-methylaspartate, 5 ml of glacial acetic acid, and a few crystals of hydroquinone was added, with stirring, 50 g (0.5 mole) of ethyl acrylate. The resulting solution was allowed to react at room temperature for 30 min and then refluxed for 24 hr. On cooling the reaction mixture was extracted with 100 ml of water. The dark orange ester layer was then diluted with 300 ml of ether and extracted successively with 100 ml each of saturated, aqueous sodium bicarbonate, water, and saturated sodium chloride solution. After drying over sodium sulfate the ether was removed and the residue was distilled to give 114.5 g (75%) of **6**: bp 120–124° (0.03 mm), n^{21}D 1.4499. The neutral oxalate, prepared by adding the base to a saturated ethereal oxalic acid solution, crystallized from ether–ethanol as white flakes, mp 90–91.5.

Anal. Calcd for $C_{30}H_{52}N_2O_{16}$: C, 51.71; H, 7.52; N, 4.02. Found: C, 51.60; H, 7.20; N, 4.12.

Di-β-carbethoxyethylmethylamine was found in the forerun from the preparation of **6**: bp 93–94° (0.5 mm), n^{21}D 1.4411 [lit.[22] bp 105–108° (3.0 mm), 136–138° (4 mm),[23] n^{20}D 1.4411[23]]. The quantity of this material obtained increased on prolonged reaction time.

1-Methyl-2,3-dicarbethoxy-4-piperidone Hydrochloride.—To a suspension of 9.6 g (0.4 mole) of sodium hydride in 550 ml of dry benzene was added, with stirring, 1.84 g (0.04 mole) of absolute ethanol. When the evolution of hydrogen ceased, the reaction mixture was heated to about 70° and 60.7 g (0.2 mole) of **6** was added dropwise at such a rate as to keep the mixture refluxing without external heating. The reaction mixture was refluxed for 30–45 min after addition was complete and then cooled to about 5°. The product was extracted from the benzene with 350 ml of cold 2 *N* hydrochloric acid with the temperature maintained at 0–5° during the process. The aqueous extract was basified to pH 8 and extracted with small portions of ether. The extractions and necessary adjustments of the pH were continued until an aliquot of the ethereal extract failed to give a positive ferric chloride test. The ether solution was dried, filtered, and evaporated giving 40.5 g (79%) of a crude product mixture which was shown by vpc analysis to contain 78% **8** and 21% **11**. Prolonged heating or standing led to the formation of more of **11**. Similar results were also obtained using sodium in toluene and sodium ethoxide in ethanol, although in the latter case the yields of **8** were considerably lower with large amounts of starting material recovered.

This product mixture was dissolved in anhydrous ether. The solution was cooled in an ice bath, and treated with dry hydrogen chloride until no further precipitation took place. The liquid layer was decanted and the residual white solid was dissolved in the minimum amount of preheated absolute alcohol and ether was added until the solution became turbid. On cooling the salt of **8** crystallized in colorless needles and the hydrochloride of **11** separated as a viscous oil. The crystals were filtered and, after washing with a cold alcohol–ether mixture, were recrystallized once more. The recrystallized salt melted at 142.5–144°.

Anal. Calcd for $C_{12}H_{19}NO_5 \cdot HCl$: C, 49.06; H, 6.86; N, 4.76. Found: C, 49.15; H, 7.02; N, 4.75.

The orange, viscous layer was collected by decantation of the solvent.

The hydrobromide of **8**, prepared in a similar manner, melted at 149–151°, the picrate melted at 95–97° (ethanol), and the perchlorate, prepared by the addition of 72% perchloric acid to an excess of the crude product in methylene chloride and evaporation of the mixture, melted at 61–63.5° (ethanol). All of these salts gave satisfactory analytical data.

1-Methyl-2,3-dicarbethoxy-4-piperidone (8).—Compound **8** was regenerated from the recrystallized salt by partitioning between ether and a cold, saturated aqueous solution of sodium bicarbonate. After the ethereal extract was dried, it was concentrated under reduced pressure. The residual oil was about 99% pure (vpc) with n^{26}D 1.4788. Nmr data are given in Table I.

1-Methyl-2,3-dicarbethoxy-4-methylamino-1,2,5,6-tetrahydropyridine (11).—Compound **11** was regenerated from the viscous, oily hydrochloride formed from treatment of the cyclization reaction products with hydrogen chloride by the same procedure used to regenerate **8** from its salt. The nmr spectrum of **11** had the following bands: δ 1.24 and 1.28 (triplets, 6 H) 4.13 (quartet, 4 H) two OCH_2CH_3, 2.41 (singlet, 3 H, NCH_3), 2.50–2.66 (multiplet 4 H), 2.82 (doublet, 3 H, C=CNHCH_3), and 8.66 [1 H, C=CN(CH_3)H].

An authentic sample of **11** was prepared by adding 0.17 g (0.0055 mole) of methylamine in absolute alcohol to a solution of 1.28 g (0.005 mole) of freshly generated **8** in 25 ml of dry benzene. After standing at room temperature for 24 hr the reaction mixture was refluxed for 30 min and the solvent was evaporated under reduced pressure. The residual oil (99% pure, vpc) had infrared and nmr spectra identical with those obtained from the material isolated from the cyclization reaction.

1-Methyl-2-carbethoxymethyl-4-carbethoxy-3-pyrrolidinone (10).—To a solution of 15.7 g (0.14 mole) of potassium *t*-butoxide in 280 ml of dry toluene, cooled to −20°, was added with stirring 30.3 g (0.1 mole) of **6** over a 30-min period. The solution was stirred at −20° for an additional 30 min and then neutralized with 26.6 g (0.14 mole) of *p*-toluenesulfonic acid monohydrate. The resulting mixture, after stirring for 10 min, was diluted with 300 ml of anhydrous ether, and the precipitated salt was removed by filtration. The filtrate, after drying over sodium sulfate, was evaporated under reduced pressure giving a residue of 23.1 g (90%). Vpc showed the presence of two major components in amounts of 28 and 58%, along with some unreacted **6**. The first component was chromatographically identical with **8**. Compound **10**, the major component, was isolated from the mixture by fractional crystallization of the hydrochloride salts from ethanol–ether. The hydrochloride gave a positive ferric chloride test and had mp 110–111°.

Anal. Calcd for $C_{12}H_{20}ClNO_5$: C, 49.06; H, 6.86; N, 4.76. Found: C, 49.10; H, 7.01; N, 4.57.

Pure **10** was liberated from this salt by neutralizing a chloroform solution of the material with triethylamine, dilution with ether, and removal of the precipitated salt. On evaporation of the solvent under reduced pressure an almost colorless oil of about 99% purity (vpc) was obtained: infrared 1701–1770 cm^{-1}; nmr δ 1.23 + 1.28 (triplet 6 H), 4.13 + 4.25 (quartet, 4 H, OCH_2CH_3), 2.40 (singlet 3 H, NCH_3), 3.50–3.65 [multiplet 2 H, CHC(=O)-CHN<], 2.50–2.80 (multiplet, 4 H, NCH_2, CH_2CO_2Et).

Registry No.—**6**, 10498-97-2; ½ oxalate of **6**, 10498-98-3; **8e**, 10498-99-4; hydrochloride of **8e**, 10499-00-0; hydrobromide of **8e**, 10499-01-1; picrate of **8e**, 10561-81-6; perchlorate of **8e**, 10499-02-2; **10k**, 10499-03-3; hydrochloride of **10k**, 10499-04-4; **11**, 10499-05-5; diethyl N-methylaspartate, 10499-06-6.

(20) All vpc determinations were carried out using an F & M Model 609 chromatograph with a 6 ft × 0.25 in. stainless steel column packed with 3% SE-30 on Fluoropak. Infrared spectra of liquids were taken as smears of the neat compounds; solids were examined as chloroform solutions. All spectra were taken using a Beckman IR-10 double-beam spectrophotometer. Nmr spectra were taken on a Varian A-60A spectrometer using $CDCl_3$ solutions with TMS as an internal standard. Elemental analysis were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium in Max Planck Institut, Mülheim (Ruhr), Germany.

(21) K. Lynch, U. S. Patent 2,438,091 (March 16, 1948).

(22) R. Mozingo and J. H. McCracken, *Org. Syn.*, **20**, 35 (1940).

(23) S. M. McElvain, *J. Am. Chem. Soc.*, **46**, 1721 (1924).