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NEW DIENAMINO ESTERS AND THEIR CYCLIZATION TO α-PYRIDONES OF NICOTINIC ACID

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Abstract—New dienamino esters (**3b-k**) were obtained by addition of enamino esters (**1b-g**) to methyl and ethyl propiolate (**2a-b**). *Z,E*-Configuration and a transoid conformation were assigned on the basis of spectral data which indicate also noncoplanarity of phenyl groups whenever present. The corresponding adducts with acetylenedicarboxylic ester (**18** and **19**) have a cisoid conformation and it was possible to differentiate between thermodynamically and kinetically controlled products. Deuteration experiments showed the existence of a 1,5-proton transfer while comparative examination of a whole series of NMR spectra furnished evidence for a head to tail attachment. Attempts to trap the intermediate zwitterion **10** resulted in the formation of **15a-b** corresponding to a cyclobutene intermediate. The reaction represents a new synthesis of the benzene nucleus and a practical method to obtain the methyltrimesic and 2,4,6-biphenyltricarboxylic acids. Additions of enamino esters to the triple bond are best interpreted as occurring through a common key intermediate, a zwitterion of type **5** or **10**. The former collapses by proton transfer and the resulting imino-derivative **6** tautomerizes to **3**. The latter cyclizes to a non-isolable cyclo-butene **12** which by opening of the ring produces the dipolar species **13** which further reacts with propiolic ester. By cyclization of the dienamino esters **3a-j** but not of **18** and **19** in dipolar aprotic solvents at 160–190° the corresponding α-pyridones **4a-f** were obtained in good yields.

Miscellaneous 1, 5 - bifunctional 5 - carbon chain compounds with carbon 1 or 5 as part of a nitrile or amide group and possessing the proper degree of unsaturation can readily undergo intramolecular cyclization to the corresponding pyridine derivatives. The unambiguous nature of the product is a distinct advantage of the 5-carbon chain cyclization in comparison with many condensations implying two or three molecules in the formation of the pyridine nucleus. Unfortunately the number of such 5-carbon chain compounds available is limited.

There is no such method for the synthesis of α-pyridones except the ring closure of glutaconic acid derivatives which results in the formation of either 6 - hydroxy - 2(1H) - pyridones[1] or of 4 - hydroxy - 2(1H) - pyridones.[2]

It has been found now that dienamino esters of the type **3** can be readily cyclized to the 2(1H)-pyridone - 5 - carboxylic esters **4** which are derivatives of the 1, 6 - dihydro - 6 - oxonicotinic acid (Scheme 1).

Dienamino esters. Dienamino esters of the type **3** (R = H in all cases) were previously obtained by Bottomley[3,4] who observed that an excess of propiolic ester reacted with primary amines at 100° to give diadducts by a two-stage mechanism.

It has been established now that the scope of this reaction is much broader, various β - amino - crotonic (**1b-c**) and -cinnamic (**1d-f**) esters reacting with propiolic ester (**2**) under mild conditions to give excellent yields of the corresponding dienamino esters **3a-k** (Scheme 1). The reaction was carried out with equimolecular amounts of propiolic ester and enamino ester either by refluxing in benzene or by heating of the reactants without solvent at 100–110°, yields being within the range of 60–85%. The addition products are crystalline substances very stable against air and moisture, which is not the case with the starting enamino esters. The new dienamino esters obtained are characterized in Table 1. The corresponding spectroscopic data are listed in Tables 2 and 3.

The structure and geometry of the dienamino esters **3** is clearly indicated by the spectroscopic measurements. The application of the Woodward-Fieser empirical rules as extended by Ostercamp[5] confirmed what was expected by examination of models, namely a transoid conformation of the diene system. The sorbic acid being taken as a parent compound (λ_{max} = 254 mμ), the addition of 65 mμ, the increment of the amino group, totalled 319 mμ in comparison with the experimental value of 325 mμ for **3b-c**. The difference of 6 mμ could be ascribed to the presence of the γ-carbethoxy group. In the same series the N-Me derivative **3d-e** has an absorption maximum of 336 mμ which is in accordance with the corresponding increment of

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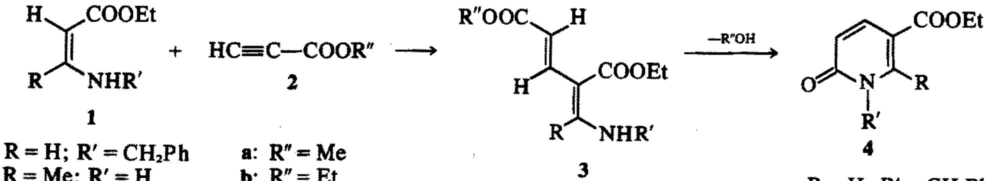


1 — a: R = H; R' = CH_2Ph; b: R = Me; R' = H; c: R = Me; R' = Me; d: R = Ph; R' = H; e: R = Ph; R' = Me; f: R = *o*-tolyl; R' = H; g: R = Ph; R' = Ph

2 — a: R'' = Me; b: R'' = Et

3 — a: R = H; R' = CH_2Ph; R'' = Et; b: R = Me; R' = H; R'' = Me; c: R = Me; R' = H; R'' = Et; d: R = Me; R' = Me; R'' = Me; e: R = Me; R' = Me; R'' = Et; f: R = Ph; R' = H; R'' = Me; g: R = Ph; R' = H; R'' = Et; h: R = Ph; R' = Me; R'' = Me; i: R = Ph; R' = Me; R'' = Et; j: R = *o*-tolyl; R' = H; R'' = Et; k: R = Ph; R' = Ph; R'' = Me

4 — a: R = H; R' = CH_2Ph; b: R = Me; R' = H; c: R = Me; R' = Me; d: R = Ph; R' = H; e: R = Ph; R' = Me; f: R = *o*-tolyl; R' = H

SCHEME 1.

Table 1. Characterization of dienamino esters **3a–k**

Compounds 3	M.p.	Recrystal. solvent	% Yield[a] (purified product)	Analyses Calc. C%	H%	N%	Found C%	H%	N%
a	109°	MeOH	70	67·30	6·98	4·61	67·18	6·97	4·45
b	108°	MeOH	75	56·32	7·09	6·56	56·59	7·12	6·42
c	110°	MeOH	80	58·18	7·49	6·16	58·23	7·64	6·20
d	68°	n-Heptane	87	58·18	7·49	6·16	57·96	7·54	6·11
e	88°	n-Heptane	85	59·73	7·94	5·80	59·60	8·05	5·73
f	123°	MeOH	70	65·44	6·23	5·09	65·26	6·29	5·12
g	149°	MeOH	68	66·42	6·62	4·84	66·44	6·79	4·72
h	99°	n-Heptane or $MeOH–H_2O$	60	66·42	6·62	4·84	66·20	6·55	5·07
i	89°	$MeOH–H_2O$	67	67·30	6·98	4·61	67·20	7·02	4·50
j	150°	MeOH	65	67·30	6·98	4·61	67·31	6·93	4·62

[a] Quantitative yields of crude products, sufficiently pure to be cyclized to α-pyridones without any further purification.

10 mμ. The NMR spectra show the two vinyl protons to be in the *trans* configuration ($J_{\alpha\beta}$ = 16 c/s) while the ν_{CO} values (1650–1669 cm^{-1}) confirm the existence of a chelated ester function adjacent to the NH group, therefore a *Z*-configuration. Further examination of the UV and NMR spectra furnished more precise details about the conformation of the aromatic dienamino esters **3f–i**. Thus the δ-phenyl groups are almost perpendicular to the plane of the molecule since no difference can be observed (Table 3) between the UV maximum absorptions when R becomes Me, Ph or *o*-tolyl.* Supplemen-

*The appreciable bathochromic effect of a coplanar phenyl group in such a system can be deduced by comparing the UV absorption maxima of the sorbic and 5-phenyl-2,4-pentadienoic acids which are 254 and 306 mμ respectively.

Table 2. PMR chemical shifts[a] of the α- and γ-ester groups of dienamino esters **3a–k**

Compounds 3	α-COOR''	γ-COOEt
a	252(q); 77(t)	257(q); 81(t)
b	225(s)	257(q); 82(t)
c	250(q); 78(t)	257(q); 81(t)
d	224(s)	257(q); 83(t)
e	251(q); 79(t)	258(q); 83(t)
f	213(s)	260(q); 83(t)
g	244(q); 68(t)	262(q); 83(t)
h	214(s)	260(q); 83(t)
i	242(q); 68(s)	260(q); 83(t)
j	239(q); 68(t)	260(q); 84(t)
k	216(s)	263(q); 84(t)

[a] In c/s at 60 Mc/s, solvent $CDCl_3$.

Table 3. UV, IR and remaining NMR data of dienamino esters **3a–k**

Compounds 3	UV λ_{max}^{EtOH} mμ (log ε)	IR (cm⁻¹)[a] ν_{CO}	IR (cm⁻¹)[a] ν_{NH,NH_2}	NMR (δ)[c] α-H[d]	NMR (δ)[c] β-H[d]	NMR (δ)[c] R	NMR (δ)[c] R′	NMR (δ)[c] δ_{NH,NH_2}
a	328(4·39); 292(4·20)	1669 1710	3295	6·02	7·43	7·30(d)	7·35(s) 4·47(d)	8·75
b–c	325(4·50); 295 sh(4·27)	1665 1703	3500[b] 3230	6·13	7·70	2·25(s)	—	broadened
d–e	336(4·50); 302 sh(4·22)	1650 1703	3135	6·12	7·80	2·28(s)	3·07(d)	10·50
f–g	328(4·36); 305 sh(4·28) 236(384)	1660 1706	3490[b] 3270	6·12	7·27	7·40(s)	—	broadened
h–i	335(4·44); 308 sh(4·27)	1651 1703	3160	6·00	7·11	7·47(m) 7·22(m)	2·70(d)	10·33
j	325(4·44); 296 sh(4·28)	1666 1704	3490[b] 3270	6·03	7·04	7·28(m) 2·23(s)	—	broadened
k	359(4·49); 294(4·28)	1652	3138	6·13	7·30	6·55–7·33(m)		11·88

[a] In CCl_4; [b] there is also an association band around 3380 cm⁻¹ which disappears on dilution; [c] in $CDCl_3$; [d] $J_{\alpha\beta}$ is invariably 15·5–16 c/s throughout the series.

tary evidence comes from the fact that the aromatic ring exerts an appreciable shielding effect on the neighbouring β-H proton (25–40 c/s). The shielding effect of the phenyl group extends still further on to either the Me or Et protons of the α-COOR″ group (6–10 c/s; Table 2 and Fig 1). On the other hand the α-H proton in **3** is shifted downfield by approximately 100 c/s in comparison with the corresponding enamino ester **1** which cannot be accounted for only by the deshielding proximity of the γ-COOEt group. This indicates that the α-position in the dienamino esters is a much less strong nucleophilic site than the corresponding position in the enamino esters.

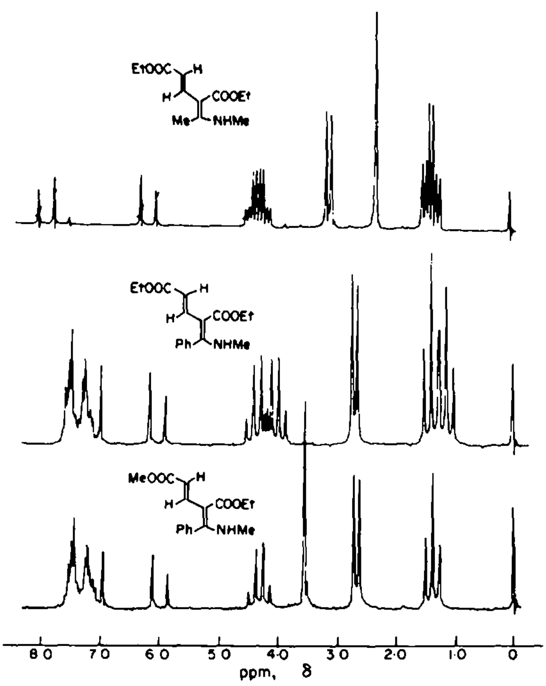
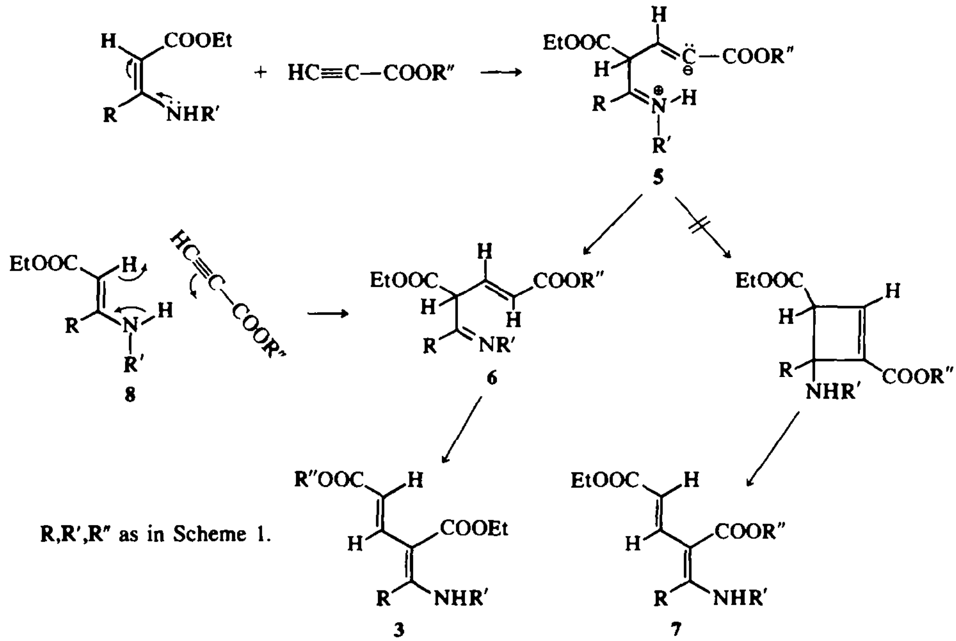


Fig 1. NMR spectra of **3e**, **3i** and **3h**.

The addition mechanism of nontertiary enamino esters to **2** deserves special attention (Scheme 2). It is known that tertiary enamines and enamino ketones react with acetylenic esters with intermediate formation of cyclobutene adducts which were isolated by Huebner *et al.*[6] and other authors.[7] Consequently Huebner *et al.* postulated that the addition of a secondary enamino ester—The ethyl β-anilinocrotonate—to dimethyl acetylenedicarboxylate proceeds by the same cyclobutene mechanism. Meanwhile they did not exclude the possibility of a Michael type of addition in view of the fact that structures of the isomeric products, which should have been obtained by the two routes, could not be distinguished spectroscopically or chemically if such be the case.

More recently Bottomley[3] outlined as probable for the addition of N-monosubstituted β-aminocrylic esters to **2**, a cyclic mechanism implying a 6-center transition state (**8**).

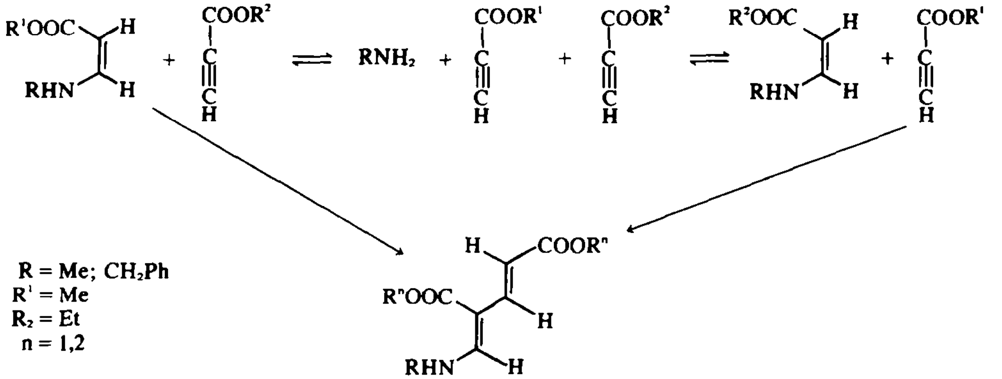
As [2s + 2s]-cycloadditions, sterically favoured in our case,[8] are thermally forbidden and also as nitrogen can stabilize formal charges, a zwitterionic mechanism without intermediate cyclization seemed more plausible. A cyclobutene mechanism would formally proceed by the insertion of the acetylene moiety while a head to tail attachment of the same to the enamino ester would take place by a zwitterionic mechanism. We were able to differentiate by NMR chemical shifts the α- and γ-carbethoxy groups so that when methyl propiolate was used as a reactant the position of the carbomethoxy group was located unambiguously—namely γ for a cyclobutene mechanism (**7**) and α for a head to tail attachment (**3**).



SCHEME 2.

A series of parallel experiments were carried out with methyl and ethyl propiolate (**2a-b**) which by addition to the same enamino ester (any of **1b–e**) gave the corresponding homologous pair of dienamino esters, respectively the pairs **3b–c**, **3d–e**, **3f–g** and **3h–i**. The NMR spectra of the ethyl propiolate adducts (Table 2) in the crotonic series show that the methylene protons of the γ-carbethoxy group are deshielded owing to H-bonding with 7 c/s in comparison with the α-carbethoxy group. This difference becomes more pronounced in the cinnamic series (18–21 c/s) where the screening effect of the noncoplanar phenyl group brings its aforementioned contribution. To a less degree the same difference can be observed between the Me protons of the carbethoxy groups (4–16 c/s). By comparing the preceding spectra with those of the corresponding methyl propiolate adducts it was possible to observe very clearly which of the two carbethoxy groups in the α- and γ-position had been replaced by the carbomethoxy group of the propiolic ester. From Table 2 and Fig 1 it can be easily seen that this is the case for the more shielded ester group namely the α-carbethoxy group. Therefore the propiolic moiety is formed by the α- and β-carbons of **3** which means that we have attachment of the propiolic ester to the enamino ester molecule rather than insertion through the intermediate of a cyclobutene adduct (**7**). The same method applied to the dienamino esters described by Bottomley[4] (**3**, R = H) gave no results since the starting β-aminoacrylic esters appreciably dissociate into propiolic ester and amine even on moderate heating (refluxing in benzene). This resulted in the impossibility of labelling the two carboxyl groups by different radicals (Et and Me) since they got mixed up in the course of the reaction, following Scheme 3, so that all the four possible esters were found in approximately equal amounts. Consequently the NMR spectrum showed the presence with equal intensities of the peaks corresponding to both carbomethoxy and carbethoxy groups located in the α- as well as the γ-position. In favour of the above equilibrium dissociation: an attempt to distill the ester **1a** *in vacuo* failed. Partial decomposition occurred with formation of benzylamine which was identified in the distillate. At the same time **2b** reacted with the remaining unchanged ester **1a** to give the corresponding dienamino ester **3a** which was the sole definite product in the residue after distillation. These observations do not confirm the conclusions drawn by Huisgen *et al.*[9] concerning the thermal stability of the β - amino - acrylic esters from the behaviour of only the piperidino- and N-cyclohexylamino derivatives. Nevertheless at normal temperatures the validity of Huisgen's *cis-trans* isomerization mechanism is not implied.

To confirm the intramolecular 1,5-proton transfer deuterated enamino esters were used in the addition reaction. Deuteration with heavy water in dry benzene of several enamino esters showed beside rapid exchange of the amino group hydrogens a more lengthy displacement by deuterium of the α-H owing to the imino-enamino tautomerism. This had been previously observed in the case of



SCHEME 3.

enamino ketones.[10] The rates were quite different from case to case. Thus appreciable deuteration of the α-position occurred for the β-anilino- crotonic and -cinnamic esters after only 2 h while in the case of **1c** only after 2 days. There was no observable deuteration of the α-position of β-aminocinnamic ester (**1d**) even after 2 days. To avoid any ambiguity, esters **1c** and **1d** were taken into consideration for our purpose. The addition of β - N - methylamino - *d* - crotonic ester to **2b** led to the formation of dienamino ester **3e** which had the α-H replaced by deuterium as expected while the β-H coupled now to α-D showed the corresponding characteristic triplet with a J_{HD} quite observable but not satisfactorily resolved. Reversely in the amino group the initial deuterium was replaced by H which had its source in the proton transfer occurring during tautomerization of the intermediate imino derivative **6**.

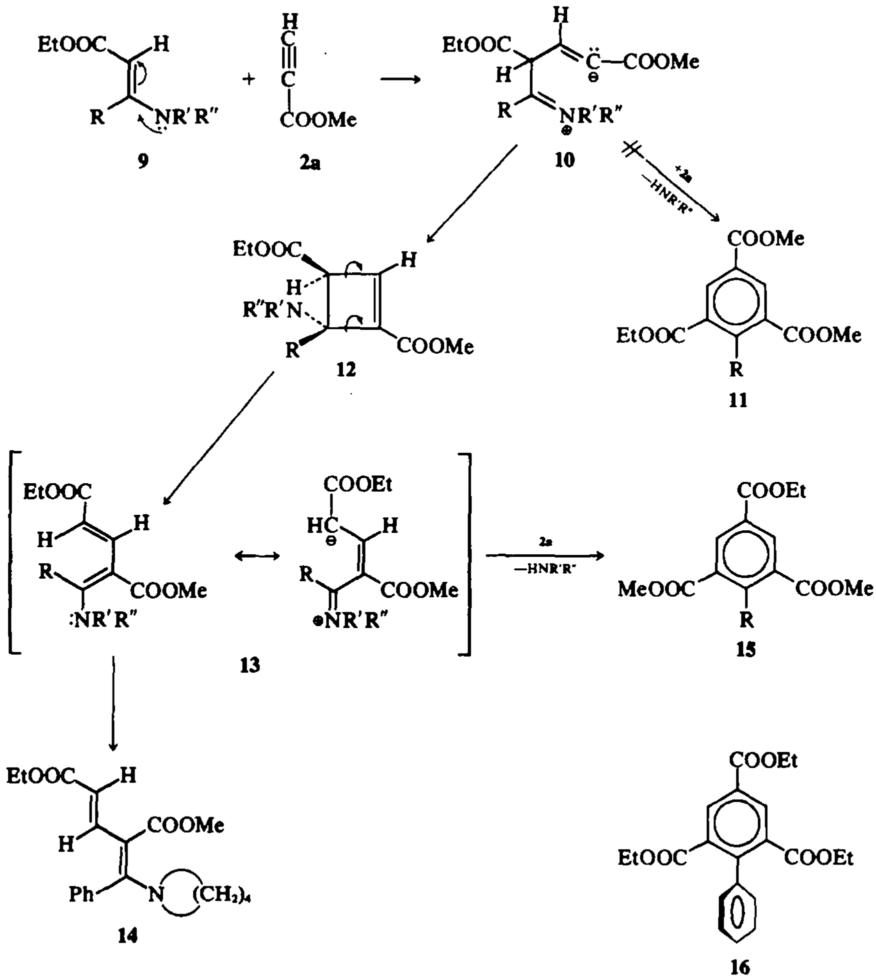
Corroborative evidence was also furnished by the fact that the tertiary enamino esters obtained by Bottomley (**9**, R = H) did not add to propiolic ester.[3] This can be rationalized by the impossibility of a proton transfer inside the zwitterion **5** with formation of an imino derivative.

Nevertheless we assumed that tertiary enamino esters of the crotonic or cinnamic series (**9a–b**) would produce a more stabilized zwitterion that could be trapped by an excess of propiolic ester. At first sight our premises were confirmed. Thus starting from ethyl β - N, N - dimethylaminocrotonate (**9a**) and methylpropiolate (**2a**) a methyltrimesic ester was obtained which was expected to have structure **11a** (Scheme 4). However no conclusions could be drawn unequivocally from the NMR spectrum about the position of the carbomethoxy and carbethoxy substituents. Therefore the same reaction was tested on the β - pyrrolidino - cinnamic ester **9b** which possesses the strongly shielding phenyl as well as the pyrrolidino group which is known to permit a very good charge separation. The results were just the reverse of our expectations: the substituted biphenyl **15b** was obtained with a symmetrical arrangement of the ester groups, namely two equivalent methyl ester groups shielded by the adjacent noncoplanar phenyl group. The triethyl ester **16** was also prepared as a model compound for the NMR chemical shifts. The above experimental data could be explained only by admitting the formation of a cyclobutene adduct **12** which by conrotatory opening of the ring gave the dipolar species **13**. The latter was trapped by the propiolic ester with the formation of a nonisolable 1,4-cyclohexadiene which aromatized to **15** by loss of one mole of amine. When working with ester **9b** it was possible to observe by NMR during the early stage of the reaction the formation of appreciable amounts of the dienaminoester **14** which gradually disappeared with formation of **15b**. No formation of dienamino ester could be observed when working with **9a**. This could be rationalized by assuming a less stronger localization of the positive charge in **13b** by resonance interaction with the phenyl nucleus.

It was possible to isolate the dienamino ester **14** as a byproduct from the mixture by column chromatography. By heating ester **14** in toluene under reflux with excess of **2a** a second crop of **15b** was obtained. The intermediate **14** could be obtained also as the main product when stoichiometric amounts of **9b** and **2a** were heated under reflux in benzene. NMR data of **14** indicate the same *Z,E*-configuration as for **3** deduced from the screening effect of the noncoplanar Ph group exerted on the α-carbethoxy and β-H substituents.

The preceding reactions represent a new synthesis of the benzene nucleus and at the same time a method of practical value to obtain methyltrimesic and biphenyl - 2, 4, 6 - tricarboxylic acids (yields around 40%).

A general examination of the mechanistic Schemes 2 and 4 indicate that a zwitterion of type **5** or **10** is the key intermediate in additions of enamino esters to the triple bond of **2**. When no proton transfer is possible cyclization to the cyclobutene adduct takes place. On the other hand the



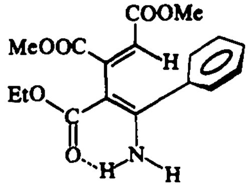
a: R = Me, R'R" = Me_2
b: R = Ph, R'R" = $-(CH_2)_4-$

SCHEME 4.

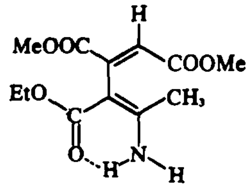
dipolar species **13a–b** which offer no possibility of a proton transfer can react with **2** while the nontertiary dienamino esters do not react with an excess of propiolic ester, the corresponding dipolar species of type **13** being easier stabilized by proton transfer to the imino derivative **17** which in its turn immediately tautomerizes to the initial dienamino ester **3** (see Scheme 5).

From the preceding discussion a certain parallelism can be concluded with the first steps of the Nenitzescu reaction, namely with the intramolecular proton transfer inside an immonium zwitterion and tautomerization of the resulting imino derivative to the corresponding enamino hydroquinone.[11] Consequently tertiary enamino esters do not react with quinones to give the corresponding tertiary enamino hydroquinones. The reasons are obviously the same.

In order to test the validity of the afore described mechanism in the case of acetylenedicarboxylic esters the additions of β - aminocinnamic (**1d**) and β - aminocrotonic (**1b**) esters were carried out. This was considered necessary since the above mentioned results of Huebner led to ambiguous conclusions. Structures *Z,Z*-**18** and *Z,E*-**19** have been assigned to the isolated adducts on the basis of their NMR, UV and IR spectra, which differ essentially from those described by Huebner as being cisoid in conformation. Both compounds in pure crystalline state possess a yellow color while the UV absorption is characteristic for a preferentially cisoid diene conformation,[12] $\lambda_{max}(\epsilon) = 389$ mμ (5760) and 361 mμ (2360) respectively. Strong evidence for the above assumption is furnished by the NMR spectrum of **18** which shows the α-H to be strongly shielded ($\delta = 5{\cdot}33$) by the noncoplanar phenyl

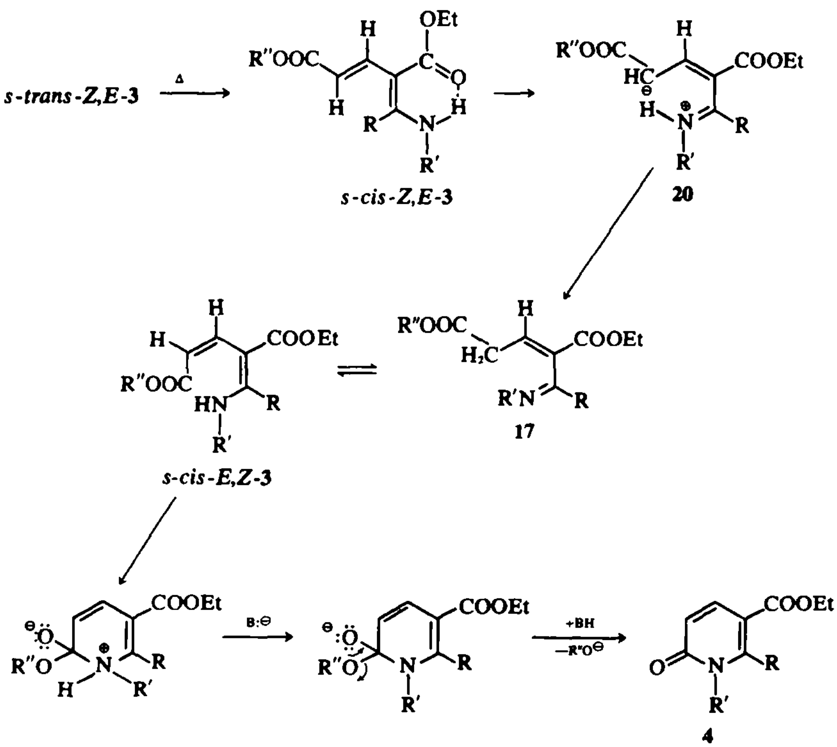


Z, Z-18



Z, E-19

group in its close proximity which is also a proof for a *Z,Z*-configuration (the corresponding values for the transoid conformations of 3a–j are in the range of 6–6·15 ppm). Examination of models showed that the strong interactions between substituents in transoid conformations are not completely avoided by cisoid conformations so that one can suppose, especially in the case of *Z,E*-19, a slight deviation from coplanarity towards a helical shape. An indication in favour of this assumption can be observed in the NMR spectrum which shows for the methylene quartet a characteristic broadening of the bands which accompanies an incipient second order splitting. The appearance of diastereotopic methylene protons could be attributed to the conformational dissymmetry of the helix since a restricted rotation should take place also in the case of *Z,Z*-18. A closer examination of the above compounds is now in progress. In the case of 19 the crude reaction product was a mixture of two isomers (5:13) which showed in the NMR spectrum an appreciable difference for the chemical shifts of the α-H ($\delta = 6{\cdot}82$ and 5·83) corresponding to the *Z,E*- and *Z,Z*-configuration. The former isomer could be isolated in pure state by elution of the mixture from a basic alumina column which produced complete isomerization of the latter. It was concluded that *Z,E*-19 was the thermodynamically stable product while the other isomer was the kinetic control product of the primary *cis*-addition. By analogy, compound *Z,Z*-18 was also considered as kinetically controlled but attempts to isomerize it were only partially successful since isolation of a pure substance was not possible owing to its alteration in the presence of acids or on the alumina column. However the addition of a trace of CF_3COOH to an NMR sample of *Z,Z*-18 permitted the observation of its complete isomer-



SCHEME 5.

ization into *Z,E*-**18**, before the altering action of the acid could take place with appreciable darkening of the solution: the shielded α-H gradually disappeared as a new peak arose ($\delta = 6{\cdot}42$).

A deuteration experiment was performed also in the case of **18**. By addition of β - amino - d_2 - cinnamic ester to acetylene - dicarboxylic ester the disappearance of the α-H was observed in the resulting **18**. This confirms the 1,5-proton transfer inside the intermediate zwitterion.

2(1H) - *Pyridone* - 5 - *carboxylic esters*. The cyclization of the dienamino esters **3a–e** was carried out by heating under reflux in dimethylformamide. More drastic conditions were necessary for the aromatic dienamino esters **3f–j**, namely heating at 180–190° in hexamethylphosphorotriamide under nitrogen or in dimethylformamide in a Carius sealed tube. In the latter case at a higher temperature of about 230° appreciable decarbethoxylation occurred with formation of the corresponding α-pyridone. The dienamino ester **3k** was the only exception, which did not cyclize and more drastic conditions resulted in the decomposition of the starting material. Attempts to cyclize the dienamino esters without a solvent or in diphenyl ether at 200° were unsuccessful.

According to these facts the cyclization mechanism appears to consist essentially in the conversion of **3** to the *s-cis* conformation which after the cleavage of the H-bonding gives the dipolar species **20** in which is possible the usual proton transfer to the imino derivative **17**, in equilibrium with several configurations of the dienamino esters **3** among which is also the *E,Z*-configuration. The latter by a base-catalyzed tetrahedral mechanism eliminates one molecule of alcohol and cyclizes to the pyridone. The cleavage of the H-bond as well as the basic catalysis explains the necessity of using such solvents as DMFA or HMPT.

Characterization, yields and purification of the α-pyridones are given in Table 4. UV and NMR data are reported in Table 5. The UV absorption maxima and intensities remain almost constant throughout the series, which is an indication of the noncopolanarity of the phenyl substituent as well as the existence in the oxo form of the N-unsubstituted α-pyridones.

The presence in the molecule of the 5-carbethoxy

Table 4. Characterization of ethyl 1,6-dihydro-6-oxonicotinates (**4c–f**)

Compounds[a] 4	M.p.[a]	Recrystal. solvent	% Yield (purified product)	Analyses Calc. C%	H%	N%	Found C%	H%	N%
c	76°	n-Heptane	80	61·52	6·71	7·17	61·77	6·83	7·01
d	191°	MeOH	86	69·12	5·38	5·76	59·34	5·55	5·82
e	79°	n-Heptane	66	70·04	5·83	5·44	70·30	6·11	5·22
f	148°	n-Heptane	88	70·04	5·83	5·44	70·19	5·85	5·38

[a] For compound **4a** elemental analysis and m.p. are given in N. Chung, H. Tieckelman, *J. Org. Chem.* **35**, 2517 (1971). See Ref 13 for compound **4b**.

Table 5. UV and NMR data of ethyl 1,6-dihydro-6-oxonicotinates (**4a–f**)

Compounds 4	UV: λ_{max}^{EtOH} mμ (log ϵ)	NMR (δ)[a] 4-H[b]	5-H[b]	OC$\underline{H}_2$CH$_3$(q)	CH$_2$C$\underline{H}_3$(t)	Others[c]
a		7·87[d]	6·58	4·30	1·32	8·24 (d, 1, 2-H) 5·11 and 7·36 (singlets, 7, PhCH$_2$)
b[e]		8·07	6·43	4·33	1·38	2·77 (s, 3, 2-Me)
c	303(3·75); 265(4·2)	7·90	6·42	4·32	1·37	2·80 (s, 3, 2-Me) 3·63 (s, 3, N-Me)
d	307(3·9); 266(4·15)	7·95	6·42	4·05	1·00	7·43 (s, 5, 2-PH)
e	307(3·85); 264(4·15)	7·99	6·62	3·98	0·95	3·22 (s, 3, N-Me) 7·32 and 7·47 (multiplets, 5, 2-Ph)
f	301(3·9); 264(4·2)	8·01	6·40	4·01	0·95	2·17 (s, 3, Ar-CH$_3$) 7·47 (m, 4, *o*-CH$_3$C$_6\underline{H}_4$)

[a] In CDCl$_3$ with TMS as internal standard; [b] doublets, $J_{4,5} = 9{\cdot}5$ c/s throughout the series; [c] the NH-proton when present very broadened; [d] quartet as coupled with both 5- and 2-H, $J_{2,4} = 3$ c/s; [e] for UV data see Ref 13.

group has the usual known[13] influence: the shorter wavelength maximum of α-pyridones shows a strong bathochromic shift while the longer one is not markedly affected. The IR spectra exhibit two strong bands at 1660 cm^{-1} and 1700 cm^{-1} which correspond respectively to the amido and ester CO groups.

One important feature of the title reaction is that no matter what kind of propiolic ester is used: methyl or ethyl, by addition of the enamino ethyl ester and cyclization, one always obtains the ethyl nicotinate. This is also unambiguous proof for the aforementioned addition mechanism. In this connection mention must be made of a recent photochemical synthesis of α-pyridones[8] starting from diphenylacetylene and N-alkyl β-aminocrotonates. The intermediate cyclobutenes and dienamino esters were not isolated but the structure of the resulting α-pyridones (yields 19–28%) indicated insertion of the acetylene moiety.

It is worthy of mention that only the dienamino adducts of propiolic esters are valuable materials for cyclization to pyridones since the acetylenedicarboxylic ester adducts cyclize to α-pyrrolidone derivatives[6] whereas the reaction between unesterified propiolic acid and β-aminocrotonic ester leads to a 1,4-dihydropyridine derivative.[14] As a matter of fact when we submitted the reaction mixtures of **18** and **19** to the aforedescribed conditions, no α-pyridones could be isolated.

EXPERIMENTAL

M. ps were taken in unsealed capillaries and are uncorrected. NMR spectra were measured with a Varian A60-A instrument and TMS as internal standard. UV spectra were determined with a Specord Carl Zeiss-Jena spectrometer and IR spectra with a UR-20 Carl Zeiss-Jena spectrometer.

Z,E - 5 - *Amino - 4 - carbethoxysorbic esters* (**3b–e**). Stoichiometric amounts (0·1 moles) of esters **1b–c**[15] and **2a–b** were refluxed in 100 ml of dry benzene for 3–5 hr. After removal of the solvent the residue was left until complete crystallization occurred. Elementary analyses and yields of recrystallization from various solvents are listed in Table 1. UV, IR and NMR data are given in Tables 2 and 3.

Z,E - 5 - *Amino - 4 - carbethoxy - 5 - phenyl - 2, 4 - pentadienoic esters* (**3f–k**). Mixtures of stoichiometric amounts (0·1 moles) of esters **1d**, **1f**,[16] **1e** or **1g**[17] and **2a–b** were heated in the absence of solvent at 100–110° in an oil bath. The reaction was complete after 2 to 3 hr. On cooling the whole mass of the corresponding esters **3f–i** crystallized, yields, elementary analyses, UV, IR and NMR data are given in Tables 1, 2 and 3.

Methyl Z,Z - 5 - amino - 4 - carbethoxy - 3 - carbomethoxy - 5 - phenyl - 2, 4 - pentadienoate (**18**). Equimolecular amounts (10 mmoles) of esters **1d** (2 g) and dimethyl acetylenedicarboxylate (1·5 g) were dissolved each in 10 ml of dry benzene. The latter soln was gradually added to the former with external cooling and the mixture was left for 24 hr at room temp. After solvent removal and trituration of the residue with CCl_4, 2 g of **18** were obtained, m.p. 108° (yield 57%). (Found: C, 61·09; H, 5·97; N, 4·26. Calcd. for $C_{17}H_{19}NO_6$: C, 61·25; H, 5·75; N, 4·20%). UV λ_{max}^{EtOH} mμ (ϵ): 389 (5835), 275 (12080), 226 (12540); IR cm^{-1} (CCl_4): 1677 (chelated CO), 1730 (CO), 3489 and 3294 (NH_2); NMR δ ($CDCl_3$): 1·23 (t, 3, $CH_2C\underline{H}_3$), 3·55 and 3·75 (singlets, 6, $COOCH_3$), 4·17 (q, 2, $OC\underline{H}_2CH_3$), 5·33 (s, 1, α-H), 7·40 (m, 5, Ph) and δ_{NH_2} very broadened in the 5–9·2 ppm region. The NMR sample of *Z,Z*-**18** on treatment with one drop of CF_3COOH showed complete transformation into the *Z,E*-**18** isomer. Characteristic feature: 6·42 (s, 1, α-H).

Methyl Z,E - *5 - amino - 4 - carbethoxy - 3 - carbomethoxysorbate* (**19**). To 1·3 g (10 mmoles) of **1b** in 10 ml benzene, 1·4 g (10 mmoles) dimethyl acetylenedicarboxylate were added with external cooling. The mixture was left over night and after removal of the solvent the crystalline residue (quantitative yield) was recrystallized from MeOH—H_2O (1 : 1). The crude product was a mixture of the two isomers, *Z,Z*- and *Z,E*-**19** in the ratio 13 : 5 which became 10 : 8 after one recrystallization as determined by NMR. By elution with $CHCl_3$ from a basic alumina column isomerization took place so that only *Z,E*-**19** was obtained which after recrystallization from cyclohexane separated as yellow crystals with m.p. 85°, 1·8 g. (Found: C, 53·42; H, 6·38; N, 5·05. Calcd. for $C_{12}H_{17}NO_6$: C, 53·16; H, 6·27; N, 5·16%); UV λ_{max}^{EtOH} mμ (ϵ): 361 (2360), 282 (13830); IR cm^{-1} (CCl_4): 1674 (chelated CO), 1720 (CO), 3503 and 3310 (NH_2); NMR δ ($CDCl_3$): 1·15 (t, 3, $CH_2C\underline{H}_3$), 1·83 (s, 3, $CH_3C{=}C$), 3·71 and 3·77 (singlets, 6, $COOCH_3$), 4·06 (q, 2, $OC\underline{H}_2CH_3$), 6·82 (s, 1, H), and δ_{NH_2} very broadened in the 5–9 ppm region. Characteristic feature of *Z,Z*-**19**: 5·83 (s, 1, α-H).

Deuteration experiments. One gram of each **1c** and **1d** was heated in dry benzene soln (5 ml) with 1 ml of heavy water. After 1 hr of manual shaking the benzene layer was separated, dried over Na_2SO_4 and the solvent removed. The oily residues formed by ethyl β-N-methylamino-*d*-crotonate and ethyl β - amino - d_2 - cinnamate were used as such in the additions reactions as described for **3b–e** and **18** respectively. After recrystallization from cyclohexane the resulting **3e**-2-*d* represented 47% of the reaction product the rest being undeuterated **3e**. The somewhat low percentage is due to the existence of a concurrent D-H exchange between the amino groups of the still unreacted **1c**-N-*d* and the resulting **3e**-2-*d*. The latter possesses an undeuterated NH group as formed by tautomerization of an imino derivative. The reaction of **1d**-N-d_2 with dimethyl acetylenedicarboxylate led to a product which after recrystallization from CCl_4 contained 62% of **18**-2-*d*, the rest being undeuterated **18**.

4 - *Carbethoxy - 2, 6 - dicarbomethoxytoluene* (**15a**). A mixture of **9a** (4 g, 25 mmoles)[15] and **2a** (5 g, 60 mmoles) was refluxed in 50 ml benzene for 5–6 hr. After solvent evaporation and trituration with EtOH, crystalline **15a** was obtained, 2·5 g (yield 40%). After recrystallization from MeOH m.p. 91°. (Found: C, 60·21; H, 5·96; Calcd. for $C_{14}H_{16}O_6$: C, 59·99; H, 5·75); NMR δ ($CDCl_3$): 1·42 (t, 3, $CH_2C\underline{H}_3$), 2·77 (s, 3, Ar—$C\underline{H}_3$), 4·13 (s, 6, $COOCH_3$), 4·43 (q, 2, $OC\underline{H}_2CH_3$), 8·54 (s, 2, Ar—H).

4 - *Carbethoxy* - 2, 6 - *dicarbomethoxybiphenyl* (**15b**). A mixture of **9b** (2·5 g, 10 mmoles) and **2a** (2 g, 22 mmoles) was refluxed for 12 hr in 20 ml toluene. After removal of the solvent the oily residue was eluted from a silica gel column with CCl_4 and 1·5 g of **15b** were obtained (yield 40%). A small sample was purified for analysis by preparative GLC. (Carlo Erba GV instrument: column 1 m/6 mm of 20% methylphenylsilicon on silanized Chromosorb W and hydrogen flow 120 ml/min). The pure

compound **15b** was a viscous oil which did not crystallize after several weeks. (Found: C, 66·89; H, 5·46. Calcd. for $C_{19}H_{18}O_6$: C, 66·65; H, 5·30); NMR δ (CCl_4): 1·43 (t, 3, $CH_2C\underline{H}_3$), 3·48 (s, 6, $COOCH_3$), 4·42 (q, 2, $OC\underline{H}_2CH_3$), 7·27 (m, 5, Ph), 8·37 (s, 2, Ar—H).

Triethyl 2, 4, 6 - biphenyltricarboxylate (**16**). The same procedure as for **15b**. (Found: C, 68·07; H, 6·14. Calcd. for $C_{21}H_{22}O_6$: C, 68·04; H, 5·99); NMR δ (CCl_4): 0·84 (t, 6, $CH_2C\underline{H}_3$), 1·43 (t, 3, $CH_2C\underline{H}_3$), 3·95 (q, 4, $OC\underline{H}_2CH_3$), 4·40 (q, 2, $OC\underline{H}_2CH_3$), 7·17 (m, 5, Ph), 8·37 (s, 2, Ar—H).

Ethyl Z,E - 4 - carbomethoxy - 5 - phenyl - 5 - pyrrolidino - 2, 4 - pentadienoate (**14**). Almost stoichiometrical amounts of **9b** (2·5 g; 10 mmoles) and **2a** (1 g; 11 mmoles) were refluxed in benzene for 10 hr. After removal of the solvent the residue was eluated from a silica gel column with CCl_4 and $CHCl_3$. The former fractions contained small amounts of **15b** while from the latter fractions the dienamino ester **14** was isolated as an orange oil which on standing crystallized with difficulty affording 1·7 g (yield 50%) with m.p. 104° after recrystallization from n-heptane. Smaller amounts of **14** could be isolated on the working-up of the reaction mixture of **15b** if elution with CCl_4 was continued with $CHCl_3$. (Found: C, 69·50; H, 7·03; N, 4·22. Calcd, for $C_9H_{23}O_4N$: C, 69·28; H, 7·04; N, 4·25%); UV λ_{max}^{EtOH} mμ (ε): 363·6 (26000), 312·5 (12050), 262·5 (7440); IR cm^{-1} (CCl_4): 1700 (CO); NMR δ ($CDCl_3$) 1·17 (t, 3, $CH_2C\underline{H}_3$), 1·88 and 3·27 [multiplets, 8, —$N(CH_2)_4$], 3·77 (s, 3, $COOCH_3$), 4·05 (q, 2, $OC\underline{H}_2CH_3$), 5·62 (d, 1, α-H), 7·10 (d, 1, β-H), 7·40 (m, 5, Ph); $J_{\alpha\beta}$ = 15·5 c/s.

Ethyl 1, 6 - dihydro - 6 - oxonicotinates **4a–c**. A soln of **3a–c** (2 g) in 25 ml dimethylformamide was refluxed for 5–6 hr. After removal of the solvent *in vacuo* the residue crystallized on standing (Table 4). Pyridone **4b** which is quite insoluble began to crystallize on cooling the mixture and after filtration a first crop was obtained (1·2 g) with m.p. 207°[13] to which a second crop was added (0·2 g) after evaporation of solvent (yield 82%); IR cm^{-1} (CCl_4) for **4c**: 1664 (CO-amide), 1707 (CO-ester).

Ethyl 1, 6 - dihydro - 6 - oxonicotinates **4d–f**. Heating at 180–190° for 3 hr was necessary so that cyclization was carried out in hexamethylphosphorotriamide under an inert atmosphere or in dimethylformamide in a sealed Carius tube: 10 ml of solvent were used for 1 g of substance. Pyridones **4d–f** separate as crystalline precipitates by addition of water to the residues left after removal *in vacuo* of the solvents (Table 4); IR cm^{-1} (CCl_4) for **4e**: 1680 (CO-amide), 1706 (CO-ester), 1730 (w); for **4f**: 1662 (CO-amide), 1710 (CO-ester), 1727 sh, 3380 (NH).

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