Mechanistic study on the formation of alkyl esters and amidoesters of (anilinomethylene)propanedioic acids by direct condensation

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SUMMARY: A series of title compounds **8** and **14** are prepared by direct condensation of ethyl orthoformate, diethyl malonate and the corresponding aniline. A study of mechanisms involved in these processes is described. The presence of Ac_2O and $ZnCl_2$ in the process of formation of diesters **8**, leads to the generation of the intermediate ethoxymethylene malonate (**6**), which then undergoes addition of the aniline. Concerning amidoesters **14**, it could be established that the formamidine was the first intermediate formed. Addition of diethyl malonate to the latter, afforded tetrahedral intermediates (e.g. **22** and **23**), which, by loosing the aniline moiety, furnished diesters **8**. Subsequently, amidoesters **14** are formed by a 1,2-addition of the aniline onto an ethoxycarbonyl group of **8**. Evidence on the aniline nucleophilicity as an important factor in the formation of **14** is provided.

INTRODUCTION

Among the azaheterocyclic antibacterial and antimalarial agents, quinoline and naphthyridine derivatives are of considerable current interest.[1] Oxolinic acid (**1**), miloxacin (**2**), chloroquine (**3**), primaquine (**4**) and quinocide (**5**),[2] are well known quinoline derivatives with biological activity.

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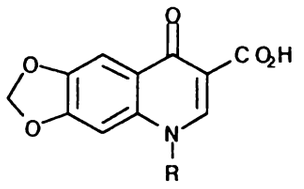
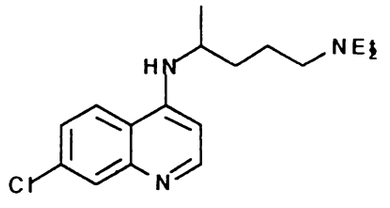


1, R = Et
2, R = OMe



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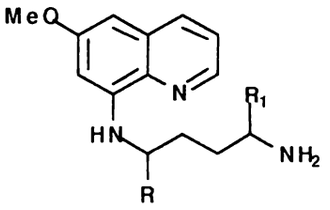
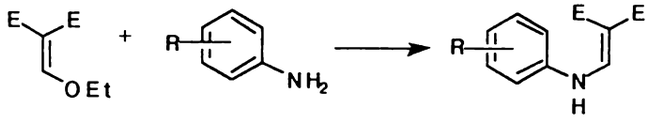
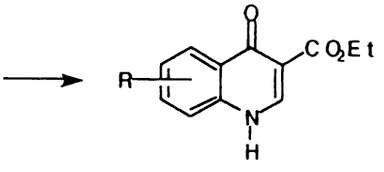


4, R = Me; R_1 = H
5, R = H; R_1 = Me

An already traditional method for the preparation of the quinoline structure consists of the condensation reaction between diethyl ethoxymethylene malonate (**6**)[3] and the corresponding aniline, **7**, followed by thermal cyclization of the afforded diethyl ester (anilinomethylene)propanedioic acid (**8**) (eq. 1).[4]

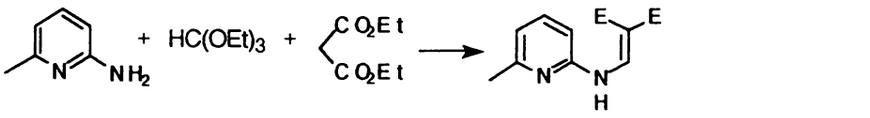


6, E = CO_2Et 7 8

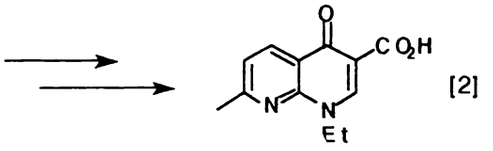


[1]

On the other hand, nalidixic acid (**9**), a potent antimicrobial, has been obtained as the cyclization product of derivative **13**. The latter was prepared by direct condensation of 6-aminopicoline (**10**), ethyl orthoformate (**11**) and diethyl malonate (**12**)[5] (eq. 2).



10 11 12 13, E = CO_2Et



[2]

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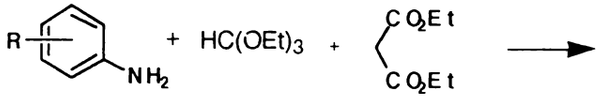
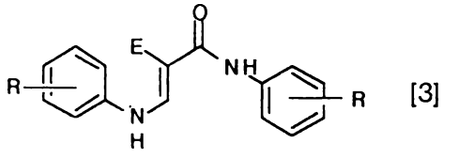
When this methodology was applied by Snyder and Jones[6] to the synthesis of quinoline derivatives, the reaction occurred readily; however, the product was not the expected diester **8**, but rather the corresponding amidoester **14c** (eq. 3). We extended this procedure to prepare a series of amidoesters in good yields (>65%)[7] (Table).



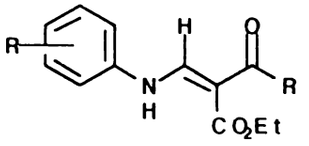
7 11 12



[3]

14

Table. Preparation of diesters (**8**) and amidoesters (**14**) of the anilinomethylene propanedioic acid.



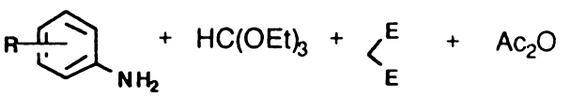
Compound	R	R'	Method[a]	m.p.(°C)	Yield(%)
8a	H	OEt	A	49-50[4b]	50
8b	*p*-Me	OEt	A	46-47[4b]	85
8c	*m*-Cl	OEt	A	50-51[4b,8]	75
8d	*m*-NO_2	OEt	A	75-76[9]	52
8e	*p*-MeO	OEt	A	38-39[10a]	69
8f	*m*-Me	OEt	A	39-40	81
8g	*p*-NO_2	OEt	A	135-136[4b]	56
14a	H	anilino	B	106-107[10]	82
14b	*p*-Me	*p*-toluidino	B	105-106	85
14c	*m*-Cl	*m*-chloroanilino	B	113-114[6,8,11]	81
14d	*m*-NO_2	*m*-nitroanilino	B	149-150	75
14e	*p*-MeO	*p*-anisidino	B	129-130[12]	67
14f	*m*-Me	*m*-toluidino	B	91-92[13]	67

[a] Method A: **11** (1.0 mol eq.), **12** (1.0 mol eq.), **16** (1.3 mol eq.) and $ZnCl_2$ (0.05 mol eq.), reflux for 5 h; then, **7** (0.66 mol eq.) and further reflux for 5 h. Method B: **7** (1.0 mol eq.), **11** (1.0 mol eq.), **12** (1.0 mol eq.) in EtOH (0.1 M), reflux for 10 h.

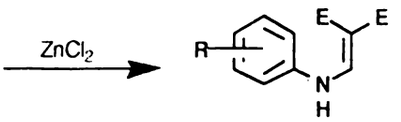
Formation of amidoesters **14** by treatment of amidines with diethyl malonate (**12**) was first described by Dains,[12] and later by Price and Roberts.[14]

More recently, Egri and col.[15] described a straighforward synthesis of 3-ethoxycarbonyl -4-hydroxyquinolines by condensation of the substituted aniline with **12** and either ethyl iminoformate[15a] or **11**.[15b]

We were able to prepare the desired compounds **8** (Table) by using Lewis acid catalysis in the direct condensation method (eq. 4).[7]



7 **11** **12**, E = CO_2Et



[4]

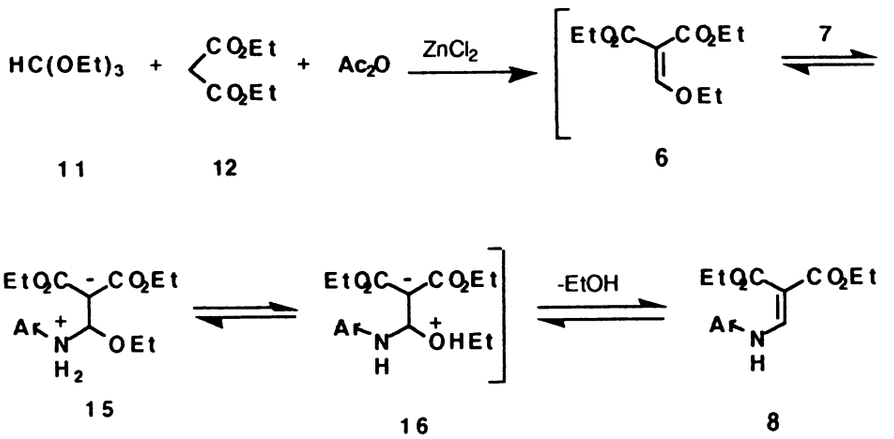
8

The present paper describes full experimental details on the preparation of compounds **8** and **14** and discloses the study of mechanisms involved in these processes.

RESULTS AND DISCUSSION

Initially, when the reaction shown in equation 4 was carried out by heating a mixture of all components, only low yields of **8** (~15%) were produced. Better results (see Table) were obtained by adding the aniline on a preheated solution of **11**, **12** and acetic anhydride in the presence of catalytic amounts of $ZnCl_2$. No traces of **14** or of cyclic product 3-ethoxycarbonyl-4-hydroxyquinoline[15c] were detected either by thin layer chromatography (*tlc*) or ^1H NMR. The main by-products were ethoxymethylene **6** and the corresponding acetanilide, formed by reaction of acetic anhydride with the aniline. The isolation of compound **6** is to be expected, as similar conditions have been used for its synthesis.[3] Indeed, a run was monitored by both ^1H NMR and *tlc*, and the mayor product that was isolated before adding the aniline corresponded to **6**. Formation of derivative **8** could then be formulated as the resultant of two steps: 1) Formation *in situ* of **6**; and 2) 1,4-addition of aniline **7** to **6**, with generation of species **15** and **16**, and loss of a mol eq. of EtOH (Scheme 1).

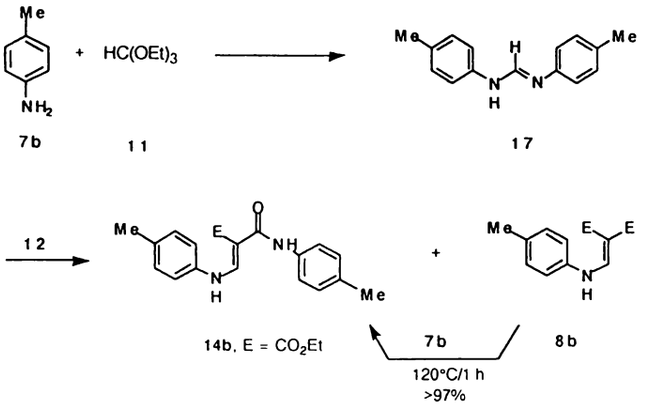
Scheme 1



Amidoesters **14** were readily obtained by heating (120°C) a mixture of **7**, **11** and **12**. In order to study the mechanism, the process was monitored by analytic *tlc*. *p*-Toluidine (**7b**) was chosen due to its relatively high reactivity and its good yield of amidoester **14b**. Thus, a rapid disappearance of **7b** and the formation of a more polar compound were observed. The latter was isolated and its structure could be established as formamidine **17**. Old reports have already shown that treatment of anilines with orthoformates and orthoacetates proceeds efficiently to give amidines.[16] Independently, we prepared **17** as white crystals by refluxing a mixture of **7b** and **11** in EtOH for 6 h (62%) (Scheme 2). When **17** was heated in the presence of **12**, amidoester **14b** and a small amount of diester

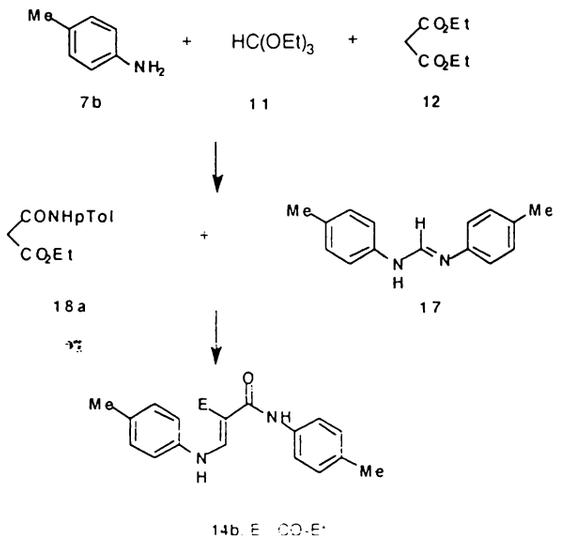
8b were isolated. This would suggest that the formamidine is an intermediate in the process,[17] and **8b** might be a second stable intermediate in amidoester formation by addition of an equivalent of the aniline to one of the ethoxycarbonyl groups.[6] In fact, amidoester **14b** could be quantitatively afforded by thermal (120°C) reaction of **8b** and **7b** for 1 h.

Scheme 2



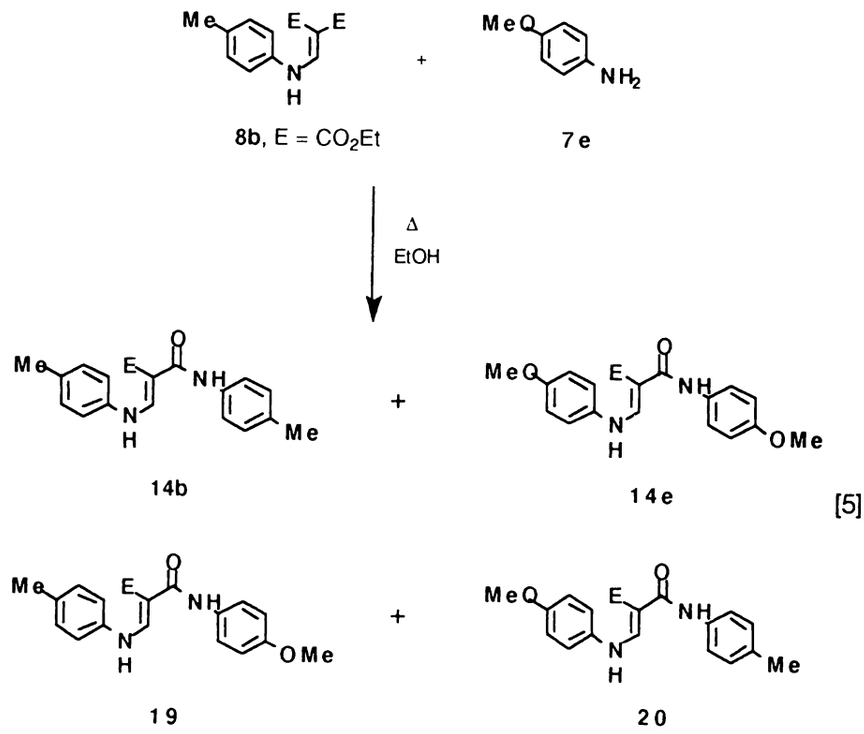
On the other hand, a fraction of amidoester **14b** could be expected to arise from condensation of formamidine **17** with ethyl *N*-*p*-tolylmalonamidate (**18a**), as suggested by Snyder and Jones.[6] Derivative **18a** would be formed by reaction of aniline **7b** and **12** under the reaction conditions (Scheme 3).

Scheme 3



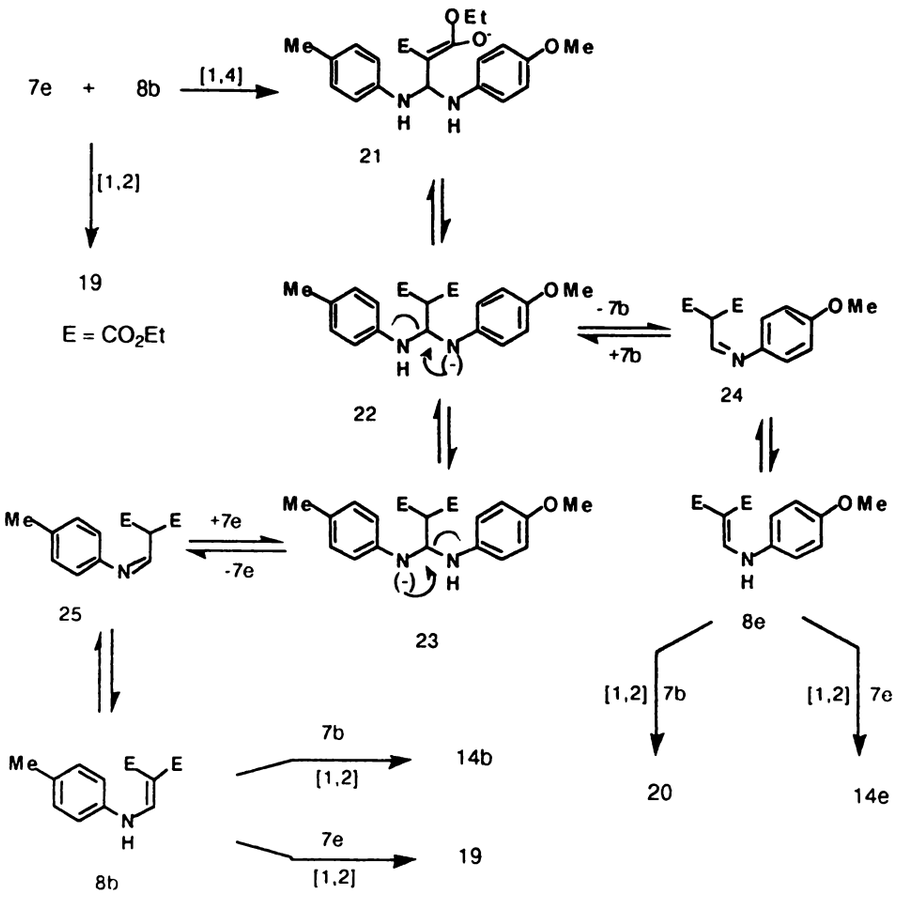
However, intermediate **18a** could not be detected in the reaction mixture, even after 90% conversion to **14b**. This suggests a very fast consumption of the aniline by reaction with **11** to give the corresponding formamidine, which would prevent any formation of **18a**.

Crossover experiments were carried out in order to get further evidence on the above results. Thus, addition of anisidine (**7e**) (1.0 mol eq.), which shows a nucleophilic strength similar to **7b**, to diester **8b** (1.0 mol eq.) and heating to 120°C for 3h, produced a mixture of amidoesters **14b**, **14e**, **19** and **20** in a ratio of 5:2.3:30:1, respectively (eq. 5).



The higher proportion of mixed amidoester **19** suggests that the 1,2-addition of aniline **7e** to diester **8b** was the main process. However, the presence of amidoesters **14b**, **14e** and **20** shows that not only a 1,2-addition took place, but that 1,4-addition of **7e** to the methylenemalonic system to form **21** was competitive. Moreover, the observation of **14e** and **20**, where the anisidyl fragment is included in the anilinomethylene skeleton, also reveals the concurrence of several equilibria (Scheme 4).

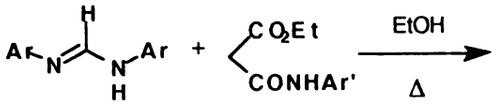
Scheme 4



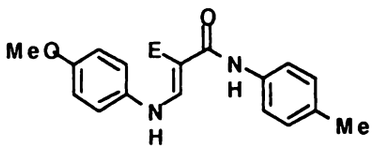
The formation of **14b** implies the presence of free *p*-toluidine (**7b**) to be formed, and upholds the idea that **22** and **23** participate as intermediates in the reaction sequence. Besides, it would account for the formation of **14e** whenever **7b** is liberated affording **8e**. This would undergo 1,2-addition either of **7e** to give **14e** or **7b** to yield **20**. A similar explanation should be formulated for the case of **14b**, in which free aniline **7b** adds to diester **8b**. In a further trial, under the same conditions, *tlc* monitoring from samples taken every 15 min, showed the presence of diester **8e** and *p*-toluidine (**7b**), as expected from the hypothesis argued and illustrated in scheme 4. Equilibria **22** ⇔ **8e** and **23** ⇔ **8b** could be established, releasing stable diesters **8b** and **8e**.

A likely *trans*-amidation by the free aniline was also considered, once the amidoester **14** was formed. This could contribute to modify the ratio of amidoesters **14b**, **14e**, **19**

and **20** in a crossover experiment as described above. In order to probe this, amidoester **18a** (1.0 mol eq.) was treated with *N,N'-bis-p*-anisidylformamidine (**26**) (1.0 mol eq.) in anhydrous EtOH (eq 6). After heating for 40 min, starting materials had disappeared



26, Ar = C_6H_4pMeO **18a**, Ar' = C_6H_4pMe

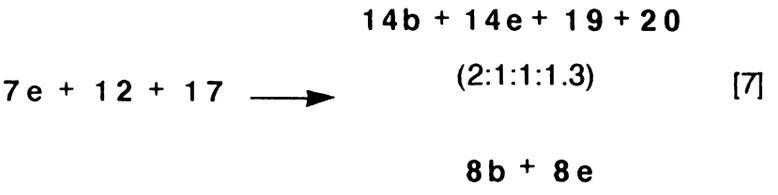


+ **7e** [6]

20, E = CO_2Et
27, E = $CONHC_6H_4pMeO$

and amidoester **20** and *p*-anisidine (**7e**) were the only products formed, even if heating was maintained for 30 min more. This makes unlikely a 1,2-addition to the amido and ester groups of the amidoester **20** and/or **18a** by the aniline present in the reaction mixture. Furthermore, an eventual ethanolysis of the amidoester groups should also be excluded, because no traces of diesters **8b** and **8e** were detected. A double amidation could be rejected too, since *bis*-amido derivative **27** could not be observed.

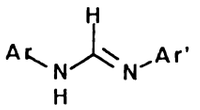
The step of addition of diethyl malonate (**12**) to the formamidine was further examined by taking an aniline like **7e** (1.0 mol eq.) and mixing it with formamidine **17** (1.0 mol eq.) in the presence of **12** (2.0 mol eq.) After heating to 120°C for 2h, a mixture of products was purified corresponding to amidoesters **14b**, **14e**, **19** and **20** in a ratio of 2:1:1:1.3, respectively (eq. 7). Diesters **8b** and **8e** were also isolated in low yield. Amidoesters **18a**



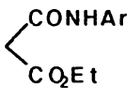
[7]

and **18b** were detected by *tlc* at the end of the process, when consumption of formamidines **26**, **28/29**[18] was almost complete. The latter were rapidly formed at the first stages of the reaction, as could be observed by *tlc* with authentic standards (see experimental). Interestingly, diester **8b** was observed earlier (30 min after starting the reaction) than **8e** (90 min, from a total of 120 min). This suggests that the addition of **12** to **17** took place

before the equilibrium between formamidines was completely established, while the concentration of **17** with respect to other formamidines **26** and **28/29** was still high.



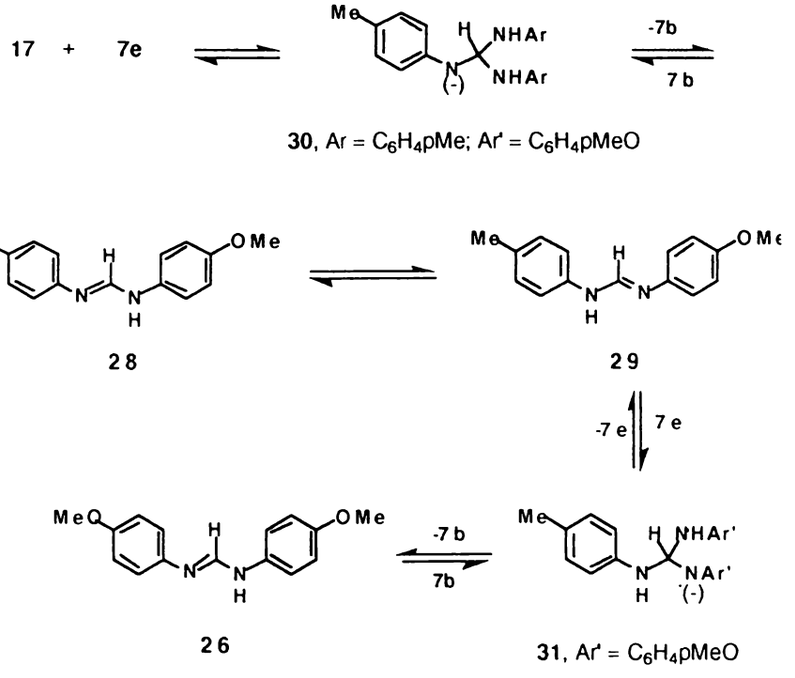
26, Ar = Ar' = C_6H_4pMeO
28, Ar = C_6H_4pMeO; Ar' = C_6H_4pMe
29, Ar = C_6H_4pMe; Ar' = C_6H_4pMeO



18a, Ar = C_6H_4pMe
18b, Ar = C_6H_4pMeO

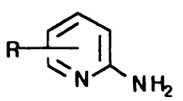
A rapid addition of **7e** to **17** would account, through a series of tetrahedral intermediates in equilibrium (e.g. **30** and **31**, Scheme 5), for the premature formation of the mixture of formamidines. This process was likely favored by the presence of traces of acid, as long as under neutral or basic conditions this rapid disproportion is avoided.[18,19] And the ratio of formamidines, according to Roberts and co-workers,[19] seems to be more influenced by statistical and steric factors than by the nucleophilicity of the anilines.

Scheme 5

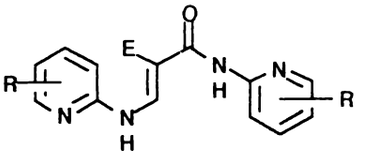


30, Ar = C_6H_4pMe; Ar' = C_6H_4pMeO
28
29
26
31, Ar' = C_6H_4pMeO

While the nucleophilicity of anilines seems not to be a determining factor for controlling the ratio of formamidines, it could be significant in the 1,2-addition process of the aniline onto an ethoxycarbonyl group of diester **8** to furnish amidoesters **14**. In fact, 2-aminopyridines (**32**), which are less nucleophilic than anilines, under direct condensation conditions in the presence of **11** and **12** do not afford amidoester **33**, unless the ethanol formed is continuously removed.[7] On the other hand, the reaction of the deactivated *p*-nitroaniline (**7g**), as shown in equation 8, after heating to ca. 130°C for 7h, gave

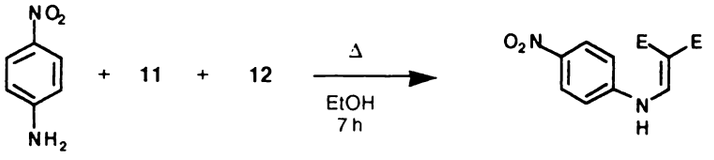


32



33, E = CO_2Et

diester **8g** in low yield (12%) together with starting material. ^1H NMR analysis of the crude did not reveal signals which could be attibuted to amidoester **14g**. Therefore, these data provide evidence that nucleophilicity is an important factor in the formation of **14**.



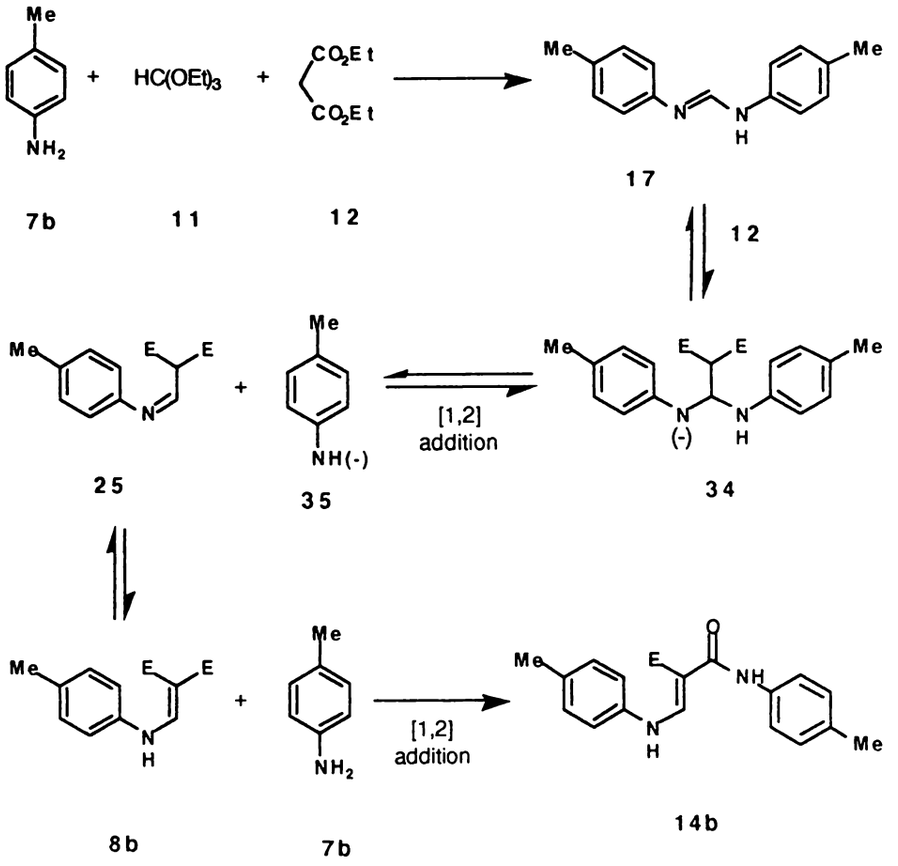
7g **8g**, E = CO_2Et [8]

The standards of formamidines, diesters and amidoesters used in this work were unambiguously prepared by direct synthesis and characterized by spectroscopic and elemental analyses (see experimental section).

Conclusions

The mechanism on the formation of amidoesters **14** is illustrated in Scheme 6: At the first stage, the aniline (e.g. **7b**) is completely consumed by forming formamidine **17**, which undergoes addition from **12** to yield tetrahedral intermediate **34**, which is in equilibrium with **8b** through species **25** and **35**. Condensation of **8b** with **7b** gives finally **14b** by a 1,2-addition process.

Scheme 6[a]



[a] E = CO_2Et

Experimental

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. Infrared spectra (IR) were recorded on a Perkin-Elmer 599B spectrophotometer. ^1H NMR spectra were obtained on Varian EM-390 (90 MHz) or Brucker AC-300P (300 MHz ^1H NMR and 75.5 MHz ^{13}C NMR) spectrometers, chemical shifts are quoted in ppm downfield from TMS as internal standard (δ, apparent multiplicity, apparent coupling constants, number of protons, and tentative structure assignment). The mass spectra (MS) were taken on a Hewlet-Packard 5985-A spectrometer in electron-impact ionization (70 eV) or chemical ionization (Cl) modes (*m/e*, rel intensity). Thin-layer chromatography (*tlc*) was done on precoated *tlc* sheets of silica gel 60 F_{254} (E. Merck) with

short-and long-wave ultraviolet light and potassium permanganate spray to visualize the spots. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Anhydrous ethanol (Baker), triethyl orthoformate and diethyl malonate (Aldrich) were used without further purification. Anilines were freshly distilled or recrystallized.

Tlc monitoring was performed at predetermined reaction times by placing the samples in a precooled (0°C) flask before applying on the chromatographic plate. Elution was done with mixtures of hexane/ethyl acetate as described in every case. Two dimensions *tlc* was carried out in order to confirm the Rf assignment.

GENERAL PROCEDURE

Preparation of **8a-8g.** A mixture of **11** (1.16 mL, 7.0 mmol), **12** (1.06 mL, 7.0 mmol), Ac_2O (0.88 mL, 9.31 mmol) and $ZnCl_2$ (46 mg, 0.34 mmol) was heated to reflux for 5 h; then, aniline **7** (4.65 mmol) was added and the reflux was continued for 5 h. The mixture was diluted with CH_2Cl_2 (40 mL) and washed successively with aqueous 5% NaOH (3 × 25 mL), aqueous 10% HCl (3 × 25 mL) and with brine until neutral. The organic extracts were combined and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel, giving the products **8a-8g**.

Anilinomethylene propanedioic acid, diethyl ester (**8a**). Column chromatography (8:2 hexane/EtOAc; Rf=0.6) and recrystallization (EtOH) afforded 0.61 g (50%) of **8a** as colorless crystals. Mp 49-50°C (lit.[4b] mp 50°C); IR (KBr): 2997, 1640, 1620, 1590, 1420, 1265, 1095, 835, 790 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.2-1.5 (m, 6H, $CO_2CH_2C\underline{H}_3$), 4.1-4.5 (m, 4H, $CO_2C\underline{H}_2CH_3$), 7.1-7.6 (m, 5H, Ph$\underline{H}$), 8.6 (d, J=14.0 Hz, 1H, C=C$\underline{H}$N), 11.1 (br d, J=14.0 Hz, 1H, PhN$\underline{H}$); MS (70 eV) 263 (M^+, 92), 218 (45), 217 (91), 174 (16), 172 (33), 162 (12), 161 (100), 144 (99), 117 (66), 104 (33), 93 (34), 77 (61).

(4-Methylanilino)methylene propanedioic acid, diethyl ester (**8b**). Column chromatography (hexane/EtOAc, 8:2) and recrystallization (C_6H_6/hexane, 2:1) afforded 1.09 g (85%) of **8b** as white needles. Rf=0.57 (8:2 hexane/EtOAc, 2×); mp 46-47°C (lit.[4b] mp 48°C); IR (KBr): 3240, 2980, 1705, 1660, 1620, 1600, 1540, 1425, 1315, 1280-1220, 1100, 1060, 840 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20-1.60 (m, 6H, $CO_2CH_2C\underline{H}_3$), 2.20 (s, 3H, Ar$C\underline{H}_3$), 4.10-4.50 (m, 4H, $CO_2C\underline{H}_2CH_3$), 6.95-7.30 (m, 2H, Ar$\underline{H}$), 8.53 (d, J=14.0 Hz, 1H, C=C$\underline{H}$N), 11.80 (br d, J=14.0 Hz, 1H, ArN$\underline{H}$); MS (70 eV) 277 (M^+, 15), 231 (17), 186 (5), 175 (11), 158 (10), 144 (4), 131 (8), 130 (9), 118 (3), 107 (9), 91 (10), 87 (10), 85 (65), 83 (100).

(3-Chloroanilino)methylene propanedioic acid, diethyl ester (**8c**). Column chromatography (8:2 hexane/EtOAc; Rf=0.45) and recrystallization (C_6H_6/hexane, 1:2) afforded 1.04 g (75%) of **8c** as colorless needles. Mp 50-51°C (lit.[8] mp 53-55°C); IR (KBr): 3260, 2990, 1720, 1690, 1660, 1620, 1600, 1420, 1270, 1090, 825, 710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20-1.50 (m, 6H, $CO_2CH_2C\underline{H}_3$), 4.10-4.45 (m, 4H, $CO_2C\underline{H}_2CH_3$), 6.90-7.40 (m, 4H, Ar$\underline{H}$), 8.45 (d, J=14.0 Hz, 1H, C=C$\underline{H}$N), 11.10 (br d, J=14.0 Hz, 1H, ArN$\underline{H}$); MS (70 eV) 297 (M^+, 19), 251 (23), 217 (9), 195 (24), 178 (21), 151 (13), 145 (10), 127 (13), 115 (29), 103 (100), 99 (29), 87 (13), 75 (38).

(3-Nitroanilino)methylene propanedioic acid, diethyl ester (**8d**). Column chromatography (hexane/EtOAc, 8:2) and recrystallization (C_6H_6/hexane, 3:1) afforded 0.74 (52%) of **8d** as pale yellow crystals. Rf=0.49 (7:3 hexane/EtOAc); mp 75-76°C (lit.[9] mp 79-81°C); IR (KBr): 3220, 2980, 1700, 1690, 1650, 1610, 1580, 1540, 1440, 1350, 1310-1250,

1120, 1040, 810, 750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20-1.50 (m, 6H, $CO_2C\underline{H}_2CH_3$), 4.10-4.50 (m, 4H, $CO_2C\underline{H}_2CH_3$), 7.20-7.65 (m, 2H, Ar$\underline{H}$), 8.50 (d, J=14.0 Hz, C=C$\underline{H}$N), 11.20 (br d, J=14.0 Hz, ArN$\underline{H}$); MS (70 eV) 308 (M^+, 44), 263 (15), 262 (45), 206 (59), 189 (24), 149 (20), 111 (15), 97 (23), 88 (63), 73 (67), 70 (100). Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.78; 5.40; N, 9.03.

(4-Methoxyanilino)methylene propanedioic acid, diethyl ester (**8e**). Column chromatography (hexane/EtOAc, 8:2) and recrystallization (C_6H_6/hexane, 3:1) afforded 0.94 g (69%) of **8e** as white needles. Rf=0.43 (8:2 hexane/EtOAc, 2×); mp 38-39°C (lit.[10a] mp 38-40°C); IR (KBr); 3280, 2980, 1720, 1690, 1650, 1620, 1518, 1410, 1305, 1260-1210, 1070, 820, 790 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16-1.50 (m, 6H, $CO_2CH_2C\underline{H}_3$), 3.85 (s, 3H, ArOC$\underline{H}_3$), 4.10-4.50 (m, 4H, $CO_2C\underline{H}_2CH_3$), 6.90-7.26 (m, 4H, Ar$\underline{H}$), 8.53 (d, J=14.0 Hz, 1H, C=C$\underline{H}$NH), 10.73 (br d, J=14.0 Hz, 1H, ArN$\underline{H}$).

(3-Methylanilino)methylene propanedioic acid, diethyl ester (**8f**). Column chromatography (8:2 hexane/EtOAc; Rf=0.5) and recrystallization (C_6H_6/hexane, 2:1) afforded 1.04 g (81%) of **8f** as white crystals; mp 39-40°C; IR (KBr): 3240, 2970, 1700-1570, 1410, 1380, 1270-1210, 1090, 830, 810 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20-1.50 (m, 6H, $CO_2CH_2C\underline{H}_3$), 2.25 (s, 3H, ArC$\underline{H}_3$), 4.06-4.50 (m, 4H, $CO_2C\underline{H}_2CH_3$), 6.80-7.40 (m, 4H, Ar$\underline{H}$), 8.58 (br d, J=14.0 Hz, 1H, C=C$\underline{H}$NH), 11.07 (d, J=14.0 Hz, 1H, ArN$\underline{H}$); MS (70 eV) 277 (M^+, 65), 232 (30), 231 (100), 186 (30), 175 (69), 158 (41), 144 (13), 131 (25), 130 (26), 118 (14), 107 (23), 91 (37), 77 (14). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.90; N, 5.05. Found: C, 64.86; H, 6.75; N, 5.16.

(4-Nitroanilino)methylene propanedioic acid, diethyl ester (**8g**). Column chromatography (hexane/EtOAc, 8:2) and recrystallization (C_6H_6/hexane, 3:1) afforded 0.80 g (56%) of **8g** as pale yellow crystals. Rf=0.62 (7:3, hexane/EtOAc); mp 135-136°C (lit.[4b] mp 142°C); IR (KBr): 3400, 2990, 1670, 1630, 1575, 1520, 1325, 1290-1250, 1130, 1055, 890, 845, 790 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20-1.60 (m, 6H, $CO_2CH_2C\underline{H}_3$), 4.15-4.55 (m, 4H, $CO_2C\underline{H}_2CH_3$), 7.32 (d, J=10.0 Hz, 2H, Ar$\underline{H}$), 8.38 (d, J=10.0 Hz, 2H, Ar$\underline{H}$), 8.60 (d, J=13.5 Hz, 1H, C=C$\underline{H}$N), 10.73 (br d, J=13.5 Hz, 1H, ArN$\underline{H}$); MS (70 eV) 308 (M^+, 22), 262 (29), 232 (10), 206 (26), 189 (14), 151 (97), 133 (100), 105 (27), 85 (23), 83 (42), 77 (34). Anal. Calcd for $C_{14}H_{19}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.47; H, 5.19; N, 8.99.

General procedure

Preparation of **14a-14f.** A solution of **11** (0.747 g, 4.67 mmol), **12** 0.691 g, 4.67 mmol) and the aniline (**7a-7f**) (4.67 mmol) in anhydrous EtOH (0.5 mL, 0.10 M) was heated to 120°C for 10 h. The residual solvent was evaporated in vacuo and the crude was purified by column chromatography on silica gel or by recrystallization, giving the products **14a-14f**.

Anilinomethylene propanedioic acid, (anilide) ethyl ester (**14a**). Recrystallization (EtOH) of the crude (pale yellow solid), afforded 1.19 g (82%) of **14a** as white crystals. Rf=0.77 (8:2 hexane/EtOAc); mp 106-107°C (lit.[9,12] mp 118°C); IR (KBr): 3450, 3250, 2980, 1715, 1680, 1600, 1580, 1440, 1280, 840, 800 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.31 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.90-7.60 (m, 10H, Ar$\underline{H}$), 8.56 (d, J=13.2 Hz, 1H, C=C$\underline{H}$N), 10.93 (br s, 1H, ArN$\underline{H}$CO), 11.80 (br d, J=13.2 Hz, 1H, ArN$\underline{H}$CH=).

(4-Methylanilino)methylene propanedioic acid, (4-methylanilide) ethyl ester (**14b**). Recrystallization (EtOH) of the crude (pale yellow solid), afforded 1.34 g (85%) of **14b** as pale yellow crystals. Rf=0.82 (8:2 hexane/EtOAc, 2×); mp 105-106°C; IR (KBr): 3200-3060, 1660, 1590, 1540, 1510, 1330, 1275, 1110, 865 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.06 (s, 3H, $ArC\underline{H}_3$), 2.25 (s, 3H, $ArC\underline{H}_3$), 4.31 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.90-7.50 (m, 8H, Ar$\underline{H}$), 8.62 (d, J=13.2 Hz, 1H, C=C$\underline{H}$N), 10.90 (br s, 1H, ArN$\underline{H}$CO), 12.60 (br d, J=13.2 Hz, 1H, ArN$\underline{H}$CH=); MS (70 eV) 338 (M^+, 21), 232 (47), 186 (53), 158 (7), 130 (9), 107 (100), 91 (12), 77 (6). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.27. Found: C, 71.06; H, 6.36; N, 8.39.

(3-Chloroanilino)methylene propanedioic acid, (3-chloroanilide) ethyl ester (**14c**). Recrystallization (EtOH) of the crude (yellow solid), afforded 1.43 g (81%) of **14c** as pale yellow crystals. Rf=0.58 (8:2 hexane/EtOAc); mp 113-114°C (lit.[8] mp 112-113°C; 113-114°C[11]); IR (KBr): 3200, 2940, 1660, 1600, 1550, 1500, 1420, 1320, 1280, 1100, 1050, 820, 730 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.26 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_2$), 6.80-7.50 (m, 7H, Ar$\underline{H}$), 7.73 (br s, 1H, Ar$\underline{H}$), 8.41 (d, J=13.0 Hz, 1H, C=C$\underline{H}$N), 11.0 (br s, 1H, ArN$\underline{H}$CO), 12.30 (br d, J=13.0 Hz, 1H, ArN$\underline{H}$CH=).

(3-Nitroanilino)methylene propanedioic acid, (3-nitroanilide), ethyl ester (**14d**). Recrystallization (EtOH) of the crude (yellow solid), afforded 1.40 g (75%) of **14d** as pale yellow crystals. Rf=0.6 (7:3 hexane/EtOAc); mp 149-150°C; IR (KBr): 3160, 2980, 1660, 1580, 1520, 1365, 1315, 1270, 1120, 830, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.30 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.30-8.05 (m, 7H, Ar$\underline{H}$), 8.46 (d, J=13.0 Hz, 1H, C=C$\underline{H}$N), 8.60 (br s, 1H, Ar$\underline{H}$), 11.23 (br s, 1H, ArN$\underline{H}$CO), 12.40 (br d, J=13.0 Hz, 1H, ArN$\underline{H}$CH=). MS (70 eV) 400 (M^+, 3), 381 (8), 308 (11), 263 (35), 262 (24), 252 (40), 206 (29), 164 (27), 139 (27), 138 (45), 119 (25), 92 (33), 69 (100).

(4-Methoxyanilino)methylene propanedioic acid, (4-methoxyanilide) ethyl ester (**14e**). Column chromatography (hexane/EtOAc, 8:2) afforded 0.385 g (67%) of **14e** as colorless crystals. Rf=0.51 (8:2 hexane/EtOAc, 2×); mp 129-130°C (lit.[12] mp 130°C); IR (KBr): 3200, 2850, 1650, 1590, 1505, 1355, 1310, 1255, 1190, 1120, 1055, 860, 820 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$, 4:1) δ 1.33 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 3.80 (s, 3H, $ArOC\underline{H}_3$), 4.23 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.70-7.20 (m, 6H, Ar$\underline{H}$), 7.50 (d, J=9.0 Hz, 2H, Ar$\underline{H}$), 8.43 (d, J=13.2 Hz, 1H, C=C$\underline{H}$N), 10.90 (br s, 1H, ArN$\underline{H}$CO), 12.30 (br d, J=13.2 Hz, 1H, ArN$\underline{H}$CH=); MS (70 eV) 370 (M^+, 17), 248 (17), 221 (2), 202 (33), 175 (5), 149 (6), 123 (100), 108 (13), 77 (3). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.98; N, 7.56. Found: C, 64.90; H, 6.04; N, 7.34.

(3-Methylanilino)methylene propanedioic acid, (3-methylanilide) ethyl ester (**14f**). Recrystallization (EtOH) of the crude (pale yellow solid), afforded 1.06 g (67%) of **14f** as white crystals. Rf=0.57 (8:2 hexane/EtOAc); mp 91-92°C (lit.[13] mp 95°C); IR (KBr): 3140, 2980, 1650, 1570, 1550, 1375, 1355, 1310, 1260, 1100, 860, 810, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.36 (s, 3H, $ArC\underline{H}_3$), 2.37 (s, 3H, $ArC\underline{H}_3$), 4.29 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.85-7.00 (m, 4H, Ar$\underline{H}$), 7.15-7.30 (m, 2H, Ar$\underline{H}$), 7.40-7.45 (m, 2H, Ar$\underline{H}$), 8.56 (d, J=13.1 Hz, 1H, C=C$\underline{H}$N),

10.93 (br s, 1H, ArNHCO), 12.30 (br d, J=13.1 Hz, 1H, ArNHCH=); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.4 (CONHAr), 167.2 (CO_2Et), 151.1 (ArNHCH=), 139.9, 139.4, 138.7, 138.2, 129.6, 128.7, 125.7, 124.5, 121.2, 118.1, 117.6, 114.2, 92.7 (=C(CO_2 Et)CON), 60.3 ($CO_2CH_2CH_3$), 21.5 ($ArCH_3$), 21.4 ($ArCH_3$), 14.5 ($CO_2CH_2CH_3$); MS (70 eV) 338 (M^+, 30), 293 (2), 232 (73), 205 (3), 186 (61), 158 (7), 130 (11), 107 (100), 91 (19), 77 (7). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.27. Found: C, 71.00; H, 6.42; N, 8.39.

General procedure

Preparation of compounds **19** *and* **20**. A solution of the α-carbethoxyacetanilide (**18a** or **18b**) (2.26 mmol), the aniline (**7b** or **7e**) (2.26 mmol) and **11** (0.367 g, 2.48 mmol) in anhydrous EtOH (1 mL) was heated to reflux for 5 h. The solvent was evaporated in vacuo and the crude was purified, giving the products **19** and **20**.

(4-Methylanilino)methylene propanedioic acid, (4-methoxyanilide) ethyl ester (**19**). Purification of the crude (pale yellow solid) by recrystallization (C_6H_6/hexane, 3:2) afforded 0.432 g (54%) of **19** as pale yellow crystals. Rf=0.73 (8:2 hexane/EtOAc, 2×); mp 158-159°C; IR (KBr): 3160, 1660, 1590, 1540, 1510, 1330, 1275, 1260, 1115, 870, 825 cm^{-1}; ^{1}H NMR (90 MHz, $CCl_4/CDCl_3$, 3:1) δ 1.40 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.43 (s, 3H, $ArCH_3$), 3.92 (s, 3H, $ArOCH_3$), 4.40 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.05 (d, J=9.6 Hz, 2H, C_6H_4Me), 7.10-7.60 (m, 4H, ArH), 7.33 (d, J=9.6 Hz, 2H, C_6H_4OMe), 8.76 (d, J=13.2 Hz, 1H, C=CHN), 10.93 (br s, 1H, ArNHCO), 12.53 (br d, J=13.2 Hz, 1H, ArNHCH=); MS (70 eV) 354 (M^+, 13), 232 (11), 186 (28), 123 (100), 108 (12), 91 (6), 65 (3). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.85; H, 6.11; N, 7.86.

(4-Methoxyanilino)methylene propanedioic acid, (4-methylanilide) ethyl ester (**20**). Purification of the crude by column chromatography (hexane/EtOAc, 8:2) afforded 0.496 (62%) of **20** as pale yellow crystals. Rf=0.68 (8:2 hexane/EtOAc, 2×); mp 109-110°C (EtOH); IR (KBr): 3200, 2960, 1650, 1620, 1580, 1600, 1510, 1325, 1260, 1110, 850 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.36 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.33 (s, 3H, $ArCH_3$), 3.83 (s, 3H, $ArOCH_3$), 4.30 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$), 6.80-7.30 (m, 6H, ArH), 7.55 (d, J=8.4 Hz, 2H, C_6H_4Me), 8.50 (d, J=13.5 Hz, 1H, C=CHN), 10.97 (br s, 1H, ArNHCO), 12.43 (br d, J=13.5 Hz, 1H, ArNHCH=); MS (70 eV) 354 (M^+, 79), 248 (90), 247 (83), 202 (99), 174 (20), 133 (23), 132 (22), 107 (100), 97 (30), 83 (30), 81 (22), 77 (20), 69 (45). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.85; H, 6.12; N, 7.80.

General procedure

Preparation of **18a** *and* **18b**. A mixture of the aniline (**7b** or **7e**) (1.87 mmol) and **12** (0.85 mL, 5.60 mmol) was heated to reflux for 4 h. The residue was purified by column chromatography of silica gel, giving the products **18a** and **18b**.

α-Carbethoxy-p-methylacetanilide (**18a**). Column chromatography (hexane/EtOAc, 8:2) afforded 0.198 g (48%) of **18a** as white needles. Rf=0.31 (8:2, hexane/EtOAc, 2×); mp

83-84°C (EtOH) (lit.[20] mp 83°C); IR (KBr): 3310, 2980,1710, 1670, 1590, 1535, 1425, 1350, 1295, 1265, 1175, 1060, 860, 735 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$, 5:1) δ 1.33 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.36 (s, 3H, $ArC\underline{H}_3$), 3.50 (s, 2H, $COC\underline{H}_2CO_2Et$), 4.29 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.18 (d, J=9.0 Hz, 2H, Ar$\underline{H}$), 7.53 (m, 2H, Ar$\underline{H}$), 9.23 (br s, 1H, ArN$\underline{H}$); MS (70 eV) 221 (M^+, 62), 199 (6), 176 (3), 134 (4), 133 (16), 108 (9), 107 (100), 106 (53), 91 (5), 77 (10). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.36; H, 6.81; N, 6.36.

α-Carbethoxy-p-methoxyacetanilide (**18b**). Column chromatography (hexane/EtOAc, 8:2) afforded 0.314 g (71%) of **18b** as white needles. Rf=0.20 (8:2, hexane/EtOAc, 2×); mp 69.5-71.0°C (EtOH) (lit.[21] mp 70-72°C); IR (KBr): 3240, 2960, 1710, 1630, 1510, 1410, 1265, 1165, 1055, 850, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 3.53 (s, 2H, $COC\underline{H}_2CO_2Et$), 3.83 (s, 3H, $ArOC\underline{H}_3$), 4.27 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.86 (d, J=9.0 Hz, 2H, Ar$\underline{H}$), 7.52 (d, J=9.0 Hz, 2H, Ar$\underline{H}$), 9.13 (br s, 1H, ArN$\underline{H}$); MS (70 eV) 237 (M^+, 96), 150 (11), 149 (69), 134 (9), 124 (10), 123 (100), 122 (27), 107 (84), 95 (11), 80 (9). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 61.00; H, 6.59; N, 5.81.

GENERAL PROCEDURE

Preparation of formamidines **17**, **26** *and* **28/29**. A solution of the anilines (**7b** and/or **7e**) (2.44 mmol) and **11** (0.722 g, 4.88 mmol) in anhydrous EtOH (2.0 mL) was heated to reflux for 6 h. The solvent was removed in vacuo and the crude was purified, giving the products **17**, **26** and **28/29**.

N,N'-bis-(p-methylphenyl)formamidine (**17**). Purification by recrystallization (EtOH) afforded 0.338 g (62%) of **17** as white crystals. Rf=0.35 (8:2 hexane/EtOAc, 2×); mp 134-135°C; IR (KBr): 3020, 2920, 1640, 1500, 1310, 1215, 840 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$, 2:1) δ 2.32 (s, 6H, $ArC\underline{H}_3$), 6.85-7.23 (m, 8H, Ar$\underline{H}$), 7.83 (br s, 1H, ArN$\underline{H}$), 8.21 (s, 1H, N=C$\underline{H}$N); MS (70 eV) 224 (M^+, 34), 118 (8), 107 (100), 106 (49), 91 (26), 84 (11), 77 (13). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.48. Found: C, 80.39; H, 7.32; N, 12.58.

N,N'-bis-(p-methoxyphenyl)formamidine (**26**). Purification by recrystallization (EtOH) afforded 0.350 g (56%) of **26** as amber-color crystals. Rf=0.15 (8:2 hexane/EtOAc, 2×); mp 115-116°C; IR (KBr): 3120, 3030, 2840, 1645, 1495, 1310, 1260, 1225, 1060, 1020, 860, 790 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$, 1:4) δ 3.76 (s, 6H, $ArOC\underline{H}_3$), 6.63-7.10 (m, 8H, Ar$\underline{H}$), 8.10 (s, 1H, N=C$\underline{H}$N), 9.33 (br s, 1H, ArN$\underline{H}$); MS (70 eV) 256 (M^+, 24), 134 (12), 124 (8), 123 (100), 108 (80), 92 (7), 77 (12). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.92. Found: C, 70.47; H, 6.23; N, 11.02.

N-(p-methylphenyl)-N'-(p-methoxyphenyl)formamidine (**28/29**). Purification by *tlc* (hexane/EtOAc, 8.5/1.5) afforded 0.22 g (37%) of **28/29** as a pale yellow oily-solid. Rf=0.17 (8:2 hexane/EtOAc, 2×); IR (KBr): 3190, 3040, 2920, 1695, 1685, 1520, 1310, 830 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$, 3:1) δ 2.35 (s, 3H, $ArC\underline{H}_3$), 3.83 (s, 3H, $ArOC\underline{H}_3$), 6.70 (m, 8H, Ar$\underline{H}$), 8.20 (m, 1H, N=C$\underline{H}$N), 8.83 (br s, 1H, ArN$\underline{H}$). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.16; H, 6.82; N, 11.79

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Resumen

Una serie de compuestos alquilésteres **8** y amidoésteres **14** fueron preparados por condensación directa del ortoformiato de etilo, malonato de dietilo y la anilina correspondiente. Se describe un estudio de los mecanismos involucrados en estos procesos. La presencia de Ac_2O and $ZnCl_2$ en el proceso de formación de los diésteres **8**, conduce a la generación del intermediario etoximetilen malonato de dietilo (**6**), el cual sufre entonces la adición de la anilina. Con respecto al mecanismo de formación de **14**, pudo establecerse que la formamidina es el primer intermediario formado, el cual sufre adición por parte del malonato de dietilo, dando intermediarios tetrahédricos como **22** y **23**. Estos pierden una molécula de anilina, produciendo los diésteres **8**. Finalmente, los amidoésteres **14** se forman por adición 1,2 de la anilina sobre uno de los grupos etoxicarbonil de **8**. Se proporcionan evidencias sobre la importancia de la nucleofilicidad de la anilina como un factor importante en la formación de los amidoésteres **14**.

References and notes

1. (a) Davidson, D.E., Jr.; Ager, A.L.; J.L.; Chapple, F.E.; Whitmire, E.E.; Rossan, R.N., *World Health Org.*, 1981, **59**, 463. (b) Albrecht, A., *Prog. Drug Res.*, 1977, **21**, 9. (c) Chu, D.T.W.; Fernandes, P.B., *Antimicrob. Agents Chemother.*, 1989, **33**, 131. (d) J.M. Domagala, J.M.; Hanna, L.D.; Heifetz, C.L.; Huff, M. P.; Mich, T.F.; Sanchez P.; Solomon, M., *J. Med. Chem.*, 1986, **29**, 394.
2. Bhat, B.; Seth, M.; Bhaduri, A.P., *Chem. Ind.*, 1983, 899; and references cited therein.
3. Parham, W.E.; Reed, L.J., *Organic Syntheses*, Collect. Vol. III. John Wiley & Sons: New York, 1955; p 395.
4. (a) Gould, R.G., Jr.; Jacobs, W.A., *J. Am. Chem. Soc.*, 1939, **61**, 2890; (b) Duffin, G.F.; Kendall, J.D., *J. Chem. Soc.*, 1948, 893.
5. (a) Ackermann, O.; Bleh, O.; Morgenstern, D.: Ger. Offen. 2,227,651 (1974), Dynamit Nobel A.-G.: Chem. Abstr. 1974, 80, 70714m; (b) Morita, Y.; Wagatsuma, K.: Japan. Kokai 88,879 (1974), Mitsubishi Chemical Industries Co., Ltd.: Chem. Abstr. 1974, **81**, 135969r.
6. Snyder, H.R.; Jones, R.E., *J. Am. Chem. Soc.*, 1946, **68**, 1253.
7. For a preliminary report, see: Muñoz, H.; Tamariz, J.; Salgado-Zamora, H.; Lázaro, M.; Labarrios, F., *Synth. Commun.*, 1987, **17**, 549.
8. Price, C.C.; Roberts, R.M., *J. Am. Chem. Soc.*, 1946, **68**, 1204.
9. Price, C.C.; Snyder, H.R.; Bullitt, O.H., Jr.; Kovacic, P., *J. Am. Chem. Soc.*, 1947, **69**, 375.
10. (a) Kermack, W.O.; Storey, N.E., *J. Chem. Soc.* 1947, 607; (b) Schofield, K.; Simpson, J.C.E., *J. Chem. Soc.*, 1946, 1033.

11. PRICE, C.C.; LEONARD, N.J.; HERBRANDSON, H.F., *J. Am. Chem. Soc.*, 1946, **68**, 1251.
12. DAINS, F.B., *Ber.*, 1902, **35**, 2496.
13. DAINS, F.B.; BROWN, E.W., *J. Am. Chem. Soc.*, 1909, **31**, 1148.
14. PRICE, C.C.; ROBERTS, R.M., *J. Am. Chem. Soc.*, 1946, **68**, 1255; also see: ROBERTS, R.M., *J. Org. Chem.* 1949, **14**, 277.
15. (a) EGRI, J.; HALMOS, J.; RAKOCZI, J. *Acta Chim.* (Budapest) 1973, **78**, 217. (b) EGRI, J.; HALMOS, J.; RAKOCZI, J., *Acta Chim.* (Budapest) 1972, **74**, 351. (c) EGRI, J.; HALMOS, J.; RAKOCZI, J., *Acta Chim.* (Budapest) 1972, **73**, 469.
16. PINNER, A., Ber., 1883, **16**, 352; also see: SHRINER, R.L.; NEUMANN, F. W., *Chem. Rev.*, 1944, **35**, 351.
17. Further evidence could be the aforementioned Dains' report which established a method to prepare amidoesters **14** by reaction of amidines with malonic esters;[12] also see references 6, 13, 14.
18. Unsymmetrical amidines were proved to exist as a tautomeric mixture, see: ONO, M.; TODORIKI, R.; TAMURA, S., *Chem. Pharm. Bull.*, 1990, **38**, 866; and references cited therein.
19. ROBERTS, R.M.; DEWOLFE, R.H.; ROSS, J.H., *J. Am. Chem. Soc.*, 1951, **73**, 2277; and references cited therein.
20. STAUDINGER, H.; BECKER, H., *Ber.*, 1917, **50**, 1016.
21. SEN, A.K.; BASU, U.P., *J. Indian Chem. Soc.*, 1957, **34**, 906.

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