Reactions of Dianions of Acyclic β-Enamino Ketones with Electrophiles. Part 5.† Esters: Synthesis of Pyridin-4-one and Pyran-4-one Derivatives

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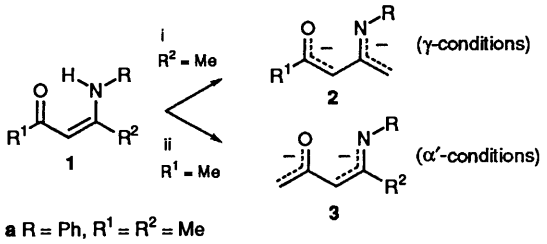
The electrophilic attack of esters to dianions of β-monosubstituted amino-α,β-unsaturated ketones and the subsequent cyclisation of the addition product offers a valuable generalisation of the synthesis of *N*-substituted pyridin-4-ones and pyran-4-ones. The reaction proceeds in good to high yields with α'-dianions. A side metallation reaction is observed with aliphatic esters. Product distribution is influenced by the nucleophilic ability of nitrogen and the electrophilicity of the carbonyl group which are involved in cyclisation. The reaction of γ-dianions with esters is the first example of a reactivity of these systems which resembles alkyl organometallic reagents more than enolates. In fact the major product of this reaction is the alcohol with incorporation of two enaminone moieties.

We have recently found the optimum conditions for the regiocontrolled metallation at the α'- and γ-positions of unsymmetrical acyclic β-monoalkylamino-α,β-unsaturated ketones.[1] The γ-dianions **2** and the α'-dianions **3** were generated by treatment of **1** with MeLi–(*N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) or lithium tetramethylpiperidide (LTMP) respectively (Scheme 1).



a R = Ph, R^1 = R^2 = Me
b R = Pr^i, R^1 = Me, R^2 = Et
c R = Pr^i, R^1 = Me, R^2 = $Ph(CH_2)_2$
d R = Pr^i, R^1 = Ph, R^2 = Me
e R = Pr^i, R^1 = R^2 = Me
f R = R^2 = Me, R^1 = Ph

Scheme 1 *Reagents and conditions:* i, MeLi–TMEDA, THF, 20 °C; ii, LTMP, THF, 20 °C

Dianions **2** and **3** react with a large variety of electrophiles such as alkyl halides,[1] oxiranes,[2] nitriles,[3] aldehydes and ketones[4] allowing the preparation of both straight chain and heterocyclic products. These promising results prompted us to investigate the reaction of γ- and α'-dianions with esters which should give 3-(*N*-substituted amino)-2-ene-1,5-diones and 5-(*N*-substituted amino)-4-ene-1,3-diones, respectively. In particular, the latter compounds would represent useful intermediates for the acid-catalysed cyclisation to *N*-substituted-pyridin-4(1*H*)-ones. This strategy has not been largely applied previously owing to the difficulty of controlling the reaction regiochemistry in the preparation of these products from triketones and amines. In fact, any of the three carbonyl groups of triketones can, in principle, react with amines leading to a mixture of diketo enamines, unless a difference is induced in the carbonyl reactivity by the nature of external groups in unsymmetrical carbonyl compounds. Indeed, to our knowledge, only the 1-phenylhexane-1,3,5-trione is reported to condense with amines exclusively at the carbonyl adjacent to the methyl group.[5] Moreover, attempted cyclisation of 5-alkylamino derivatives is reported to lead to pyranones instead of the expected pyridinones.[5] Alternative *in situ* formation of diketo enamines from the reaction between pyranones and amines *via* ring opening followed by recyclisation[6] to pyridinones is restricted by the availability of the starting material, whose more convenient synthesis is the cyclisation of 1,3,5-triketones.[7] Finally, a synthesis of pyridinones *via* enamino ketones has been described based on acylation of styrylamines with acyl chloride, which allowed the preparation of a large variety of 1-alkyl-3,5-disubstituted pyridin-4(1*H*)-ones, but in not very high yield and by a somewhat complex procedure.[8]

In this paper, the results of the reaction of α'- and γ-dianions of unsymmetrical acyclic β-monosubstituted amino-α,β-unsaturated ketones with esters are reported.

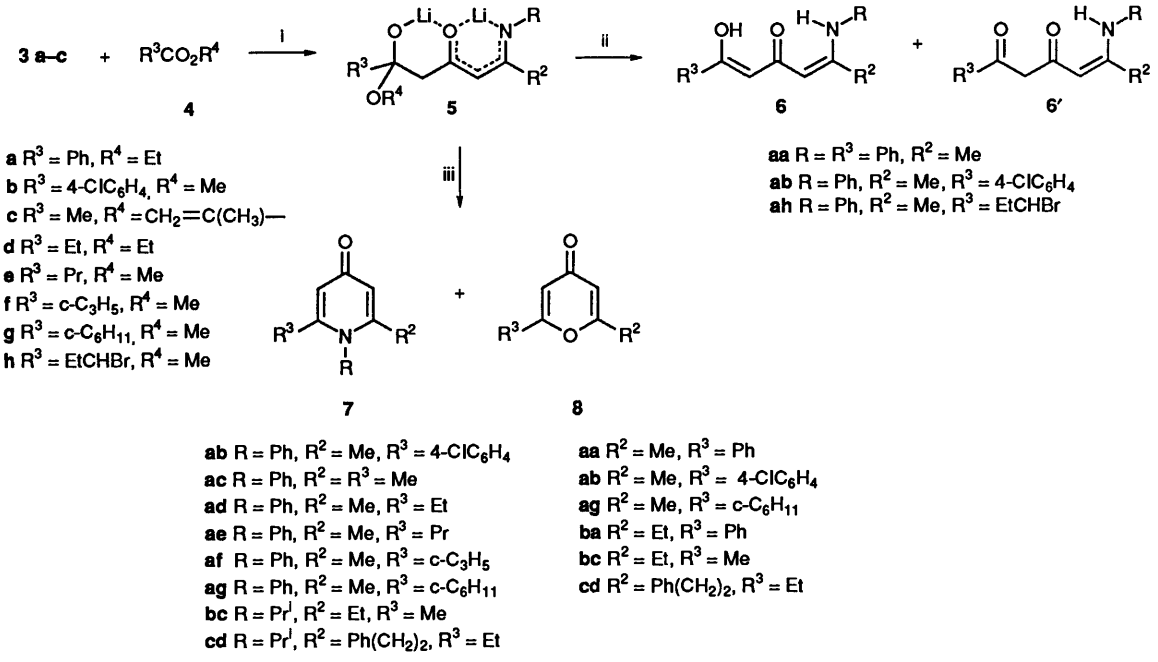
When a tetrahydrofuran (THF) solution of an ester **4** is added to a cold (−50 °C) solution of the α'-dianion **3**, prepared according to the previously reported procedure,[1] and then allowed to react for a few minutes, the quenching of the reaction with saturated aqueous ammonium chloride gives the expected compounds **6** (Scheme 2).

Yields are very high with aryl esters. In fact, ethyl benzoate **4a** and methyl 4-chlorobenzoate **4b** react with the α'-dianion **3a** giving enamino diones **6aa** and **6ab** in 88 and 86% yields respectively.

In contrast, the treatment of **3a** with methyl 2-bromobutyrate **4h** gives the corresponding compound **6ah** in 32% yield together with a 40% yield of the starting enaminone and traces of ester self-condensation product. Longer reaction times do not lead to higher yields of enamino dione, but instead an increase of ester self-condensation product is noted. Lower yields were always obtained in reactions with aliphatic esters than with aromatic ones; this has been interpreted in terms of a side transmetallation reaction which occurs between the α'-dianion and esters having acidic hydrogens at the α position.

It is worthy of note that 2-bromobutyrate shows preferential attack at the ester function rather than bromine nucleophilic displacement. NMR spectra of products **6** show that they exist in solution as a mixture of tautomers with the prevalence of the enol **6** over the diketo enamine **6'** form (the ratio **6** *vs.* **6'** being 7:1, 2:1 and 2.5:1 for **6aa**, **6ab** and **6ah** respectively). Moreover, it was observed that products **6** arising from aliphatic esters

† Part four: ref. 4.

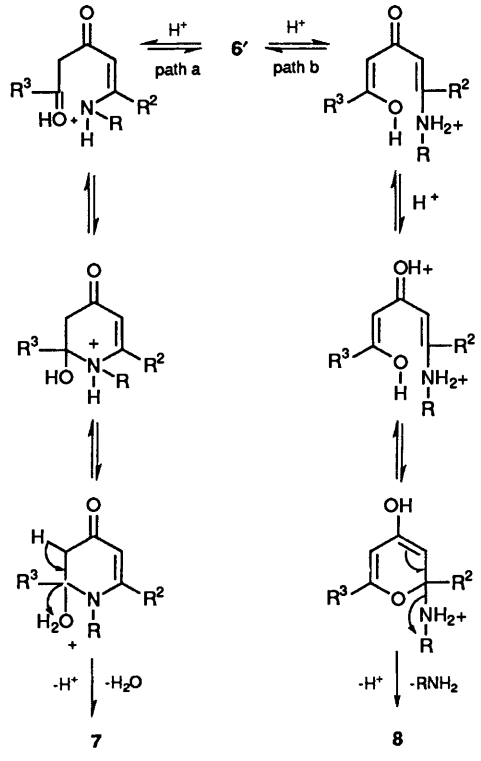


Scheme 2 *Reagents and conditions:* i, THF, −50 °C; ii, NH_4Cl; iii, H^+

could undergo to some extent decomposition both with time and in solution. Since the principal aim of the present work was the investigation of new methods for generating heterocyclic systems, in further experiments enamino diones were not isolated and the reaction mixture was immediately submitted to cyclisation conditions.

Enamino diones such as **6'** can conceivably undergo two types of acid catalysed cyclisation leading either to pyran-4-ones or to *N*-substituted pyridin-4-ones[5] (Scheme 3).

Several mineral and Lewis acids were thus tested to find conditions suitable to address cyclisation towards pyranones or pyridinones. Over many unsuccessful attempts which led to



Scheme 3

Table 1 Reaction between the α'-dianions **3** and esters **4** in THF at −50 °C for 15 min followed by acid catalysed cyclisation

				Yield (%)		
Entry	Dianion	Ester	Acid	**1**[c]	**7**	**8**
1	**3a**	**4b**	PPA[a]	—	57 (**ab**)	21 (**ab**)
2	**3a**	**4c**	PPA[a]	35 (**a**)	53 (**ac**)	—
3	**3a**	**4d**	PPA[a]	40 (**a**)	43 (**ad**)	—
4	**3a**	**4e**	PPA[a]	27 (**a**)	49 (**ae**)	—
5	**3a**	**4f**	PPA[a]	30 (**a**)	64 (**af**)	—
6	**3a**	**4g**	PPA[a]	43 (**a**)	50 (**ag**)	—
7	**3b**	**4a**	PPA[a]	—	—	70 (**ba**)
8	**3b**	**4c**	PPA[a]	53 (**b**)	20 (**bc**)	17 (**bc**)
9	**3c**	**4d**	PPA[a]	53 (**c**)	13 (**cd**)	5 (**cd**)
10	**3a**	**4a**	HCl[b]	—	—	77 (**aa**)
11	**3a**	**4b**	HCl[b]	—	—	63 (**ab**)
12	**3a**	**4g**	HCl[b]	45 (**a**)	37 (**ag**)	15 (**ag**)
13	**3b**	**4a**	HCl[b]	—	—	74 (**ba**)
14	**3b**	**4c**	HCl[b]	54 (**b**)	—	30 (**bc**)
15	**3c**	**4d**	HCl[b]	55 (**c**)	—	34 (**cd**)

[a] Overnight at 70 °C. [b] Bubbled into the mixture for 2 h. [c] Recovered as 1,3-diketone

multicomponent, inseparable mixtures, treatment of the crude reaction with hot polyphosphoric acid (PPA) offered the best conditions to obtain pyridin-4-ones, while formation of pyran-4-ones was found to be favoured by directly bubbling anhydrous hydrogen chloride into the reaction mixture solution. Under these conditions the two cyclisation courses occur in high yields based on the enaminone used minus the amount recovered. Results obtained are reported in Table 1.

Cyclisation of diketo enamines by means of hot PPA to form *N*-arylpyridin-4-ones has been reported in the literature.[5] However, some significant differences from previously reported results have to be reported for the reaction carried out with the present one-pot procedure. Reaction between the α'-dianion of 4-anilinopent-3-en-2-one **3a** and methyl 4-chlorobenzoate **4b**, exclusively leads to pyran-4-one **8ab** in 63% yield if cyclisation is effected with gaseous HCl, while a 57% yield of pyridin-4-one **7ab** and a 21% yield of **8ab** are obtained by cyclisation with PPA. On the other hand, reaction between **3a** and methyl

cyclohexanoate **4g** exclusively gives pyridin-4-one **7ag** if cyclisation is effected with PPA, but a 37% yield of **7ag** and a 15% yield of **8ag** by cyclisation with HCl. Similarly, treatment of **3a** with isopropenyl acetate **4c** exclusively gives the pyridinone **7ac** in 53% yield when PPA is used while treatment of the same ester **4c** with 4-(isopropylamino)hex-3-en-2-one **3b**, in the same PPA conditions, gives a mixture of 17% of pyranone **8bc** and of 20% of pyridinone **7bc**. Finally from treatment of **3b** with ethyl benzoate **4a**, the exclusive formation of pyranone **8ba** is obtained by cyclisation with PPA. These findings suggest that at least two factors influence the course of the cyclisation reaction, closely linked to the electrophilicity of the carbonyl group and to the basicity of the enaminic nitrogen. As depicted in Scheme 3 a competition exists between protonation and nucleophilic ability of the amino moiety depending on the nature of the amino substituent and on the acid strength.

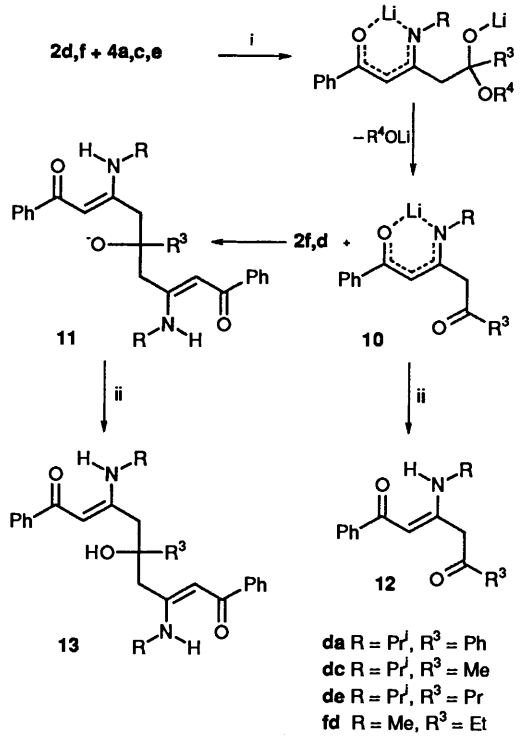
When R = Ar, PPA is too weak an acid for an extensive protonation of the amino nitrogen. Therefore, when R^3 = alkyl, the nucleophilic attack at the carbonyl function can easily occur and pyridinone is obtained travelling path a of Scheme 3 (Table 1, entries 2–6). On the other hand, when R^3 = Ar, the formation of both compounds may be ascribed to a lesser electrophilicity of the carbonyl group (Table 1, entry 1). When R = alkyl, the amino nitrogen is much more basic and therefore path b of Scheme 3 should be favoured. In fact in this case for R^3 = Ar the exclusive formation of pyranone (Table 1, entry 7) and for R^3 = alkyl a mixture of both compounds (Table 1, entries 8, 9) respectively, is observed. The higher strength of gaseous anhydrous hydrogen chloride accounts for the exclusive formation of pyranones *via* path b (Table 1, entries 10, 11, 13–15). In fact, a more extensive (less reversible) protonation of both alkyl and aryl amino nitrogen in **6′** can be effected by HCl rather than by PPA. Further protonation of the carbonyl oxygen leads to a dicationic intermediate from which ring closure to pyranone can occur through an intramolecular nucleophilic attack of the enolic oxygen to the enaminic carbon followed by amine removal. An alternative route to pyranones *via* removal of amino group to give triketones which easily undergo acid-catalysed cyclisation[9] cannot be ruled out. However, as a plausible support to the mechanism described above, competition of path a with path b has been observed also in HCl cyclisation conditions, at least in the only case of R = aryl and R^3 = alkyl (Table 1, entry 12) in which unfavourable conditions to obtain pyranones are set up by the concomitance of low basicity of the amino nitrogen and high electrophilicity of the carbonyl.

In no reactions were *N*-substituted anilines found arising from a hypothetical cyclisation at the carbon atom, even when a bulky isopropyl group is linked to the nitrogen atom. It is in fact reported[10] that in this case the very related adducts arising from pyrylium salts and primary amines give a large predominance of benzenoid rings instead of heterocyclic rings. Very likely in the boat-shaped pyridinone skeleton, bulky *N*-substituents are better arranged than in the planar pyridine ring.

The treatment of an ester **4** with a γ-dianion **2** at −50 °C, followed after a few minutes by quenching with saturated aqueous ammonium chloride afforded the expected 3-(alkylamino)-2-ene-1,5-dione **12** in poor yields, the alcohol **13** arising from incorporation of 2 mol equiv. of enaminone being the major product (Scheme 4).

Modifications of the reaction conditions, of the metallating agent used to generate **2** and of the steric hindrance on the γ-position do not significantly influence the product distribution (Table 2).

This different behaviour in reactivity of α′- and γ-dianions with esters can be explained in terms of the different stability in solution at low temperature of the adduct formed by addition to the ester of α′ or γ-carbanion respectively. In fact, the adduct



Scheme 4 *Reagents and conditions:* i, −50 °C, THF; ii, NH_4Cl

from the α′-dianion can be stabilised in a bridged conformation like **5** (see Scheme 2) in which lithium atoms interact with both external hemiacetalic and central carbonyl oxygens, giving rise to a stable six-membered ring. From such a structure expulsion of the alkoxy ion to give enamino diones **6′** is allowed only after acidic quenching. As far as the stability of the analogous adduct from the γ-dianion is concerned, a remarkable structure difference from the α′-dianion derived adduct must be taken into account. In this case, in fact, nitrogen, which is in the middle of the structure, can only coordinate to one lithium, the R group on nitrogen preventing coordination of a second lithium. In these conditions it is reasonable to assume that lithium coordination exclusively occurs between nitrogen and the enaminonic oxygen, thus allowing a pseudoaromatic array of the enaminonic site of the system. In consequence, a stabilisation similar to **5** cannot be set up in the adduct from addition of esters to the γ-dianion, which, instead, immediately transforms into the intermediate anion **10** by expulsion of the alkoxy ion. In **10** the carbonyl in the δ position does not feel the effect of the negative charge delocalized along the enaminonic moiety of the molecule and behaves as an isolated carbonyl function. In consequence it can undergo immediate attack of another molecule of γ-dianion to give adduct **11** which accounts for large amount of the alcohol **13** recovered after work-up of the reaction with respect to the enamino dione **12**.

To support the reaction pathway discussed above and to show that an intermediate like **10** was effectively involved in it, experiments were performed using MeLi in the presence of TMEDA to generate the γ-dianion. Product distribution was not modified by the presence of a strong lithium complexing agent like TMEDA when 2.5 equiv. of base were used (see Table 2), while 5-hydroxy-3-(isopropylamino)-1,5-diphenylhex-2-en-1-one **14** was recovered in 94% yield from a reaction carried out with a large excess of MeLi which is a more nucleophilic reagent than the enaminone γ-dianion.

In conclusion, the reaction of dianions of β-monosubstituted-amino-α,β-unsaturated ketones with esters is the first example of a different reactivity of α′- and γ-positions. The reaction of α′-dianions offers a valuable entry to *N*-substituted-pyridin-4-

Table 2 Reaction between γ-dianions **2** and esters **4** under various conditions

Dianion	Base	Ester	Conditions		Yield (%)	
			T/°C	*t*/min	**12**	**13**
2d	LTMP (2.5 equiv.)	**4a** (1.5 equiv.)	0	5	16	80
2d	LTMP (2.5 equiv.)	**4a** (1.5 equiv.)	−50	5	27	63
2d	LTMP (2.5 equiv.)[a]	**4a** (1.5 equiv.)	−50	5	24	71
2d	LTMP (4 equiv.)	**4a** (3 equiv.)	−50	5	20	77
2d	MeLi–TMEDA (2.5 equiv.)	**4a** (1.5 equiv.)	−50	30	11	84
2d	MeLi–TMEDA (4 equiv.)	**4a** (3 equiv.)	−50	30	—[b]	—
2d	LTMP (2.5 equiv.)	**4c** (1.5 equiv.)	−50	5	6	86
2d	LTMP (2.5 equiv.)	**4e** (1.5 equiv.)	−50	5	30	57
2f	LTMP (2.5 equiv.)	**4d** (1.5 equiv.)	−50	5	6	76

[a] Dropping the dianion solution into the cooled ester solution. [b] 94% 5-hydroxy-3-(isopropylamino)-1,5-diphenylhex-2-en-1-one **14**

ones and pyran-4-ones. This reaction represents a wide generalisation of the previous[5,8] report on the cyclisation of diketo enamines, since a large variety of substituents can be placed in *N*-, 2- and 6-positions and, in principle, in positions 3- and 5- as well, thus allowing the synthesis of many so far unknown pyranone and pyridinone derivatives. Otherwise, reactivity exploited by γ-dianions exclusively resembles that of alkyl organometallic reagents.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz or a Varian T 60 (60 MHz) spectrometer in $CDCl_3$ solutions. Chemical shifts are given in ppm from $SiMe_4$. Coupling constants are given in Hz. Melting points are uncorrected. Mass spectra were determined by the electron impact method on a VG 7070 instrument. GC analyses were performed on a GC–MS Hewlett-Packard 59970 work station. IR spectra were recorded on a Perkin-Elmer 1600 FTIR apparatus. THF was dried by refluxing over sodium wire until the blue colour of benzophenone ketyl persisted and then distilled into a dry receiver under a nitrogen atmosphere. LTMP was prepared by mixing equimolecular amounts of butyllithium and amine in THF at 0 °C. Commercial methyllithium solutions (Aldrich) were employed under a dry atmosphere and were titrated before use. Commercial compounds (Aldrich) were distilled and dried over molecular sieves before use.

4-Anilinopent-3-en-2-one **1a** was synthesised according to Boatman and Hauser's procedure.[11] 1-Phenyl-3-(isopropylamino)but-2-en-1-one **1d** and 4-(isopropylamino)pent-3-en-2-one **1e** were synthesised according to Singh and Tandon's procedure.[12] 4-(Isopropylamino)hex-3-en-2-one **1b** and 6-phenyl-4-(isopropylamino)hex-3-en-2-one **1c** were prepared from the γ-dianion of **1e** and the appropriate bromide according to our procedure.[1] γ- And α′-dianions were prepared as previously described.[1] The homogenity of the sample of new compounds was confirmed by TLC and GC–MS analysis before submission to exact mass determination.

Reaction of the α′-Dianion with Esters.—Linear products. A THF solution of the appropriate ester **4** (6 mmol) was added to a cooled (−50 °C) solution of the α′-dianion **3** (5 mmol) and the mixture was stirred for 15 min under a nitrogen atmosphere. The solution was then poured into saturated aqueous ammonium chloride and extracted with Et_2O. The organic layer was dried, evaporated under reduced pressure and the residue was chromatographed on a silica gel column (hexane–Et_2O, 3:2 as eluent) to isolate compounds **6**. Yields and physical data are reported below.

5-Anilino-1-phenyl-hex-4-ene-1,3-dione **6aa**. 88%; m.p. 100–101 °C (lit.,[5] 98–99 °C); δ_H(200 MHz) appears as a 7:1 mixture of enol and keto tautomers; keto tautomer δ 1.98 (s, 3 H, Me), 4.02 (s, 2 H, CH_2), 5.28 (s, 1 H, CH=), 7.10–7.90 (m, 10 H, ArH) and 12.20 (br s, 1 H, NH); enol tautomer δ 2.06 (s, 3 H, Me), 5.06 (s, 1 H, CH=), 5.87 (s, 1 H, CH=), 7.10–7.90 (m, 11 H, ArH + OH) and 11.98 (br s, 1 H, NH).

5-Anilino-1-(4-chlorophenyl)hex-4-ene-1,3-dione **6ab**. 86%; m.p. 108–110 °C; δ_H(200 MHz) appears as a 2:1 mixture of enol and keto tautomers; keto tautomer δ 1.96 (s, 3 H, Me), 3.96 (s, 2 H, CH_2), 5.24 (s, 1 H, CH=), 7.00–7.50 (m, 7 H, ArH), 8.00 (d, *J* 10, 2 H, ArH) and 12.36 (br s, 1 H, NH); enol tautomer δ 2.05 (s, 3 H, Me), 5.03 (s, 1 H, CH=), 5.81 (s, 1 H, CH=), 7.00–7.50 (m, 8 H, ArH + OH), 7.70 (d, *J* 10, 2 H, ArH) and 11.94 (br s, 1 H, NH); $\nu(CCl_4)$/cm^{-1} 1579 (C=O); *m*/*z* (%) 315 (M^+ + 2, 11), 313 (M^+, 36), 223 (29), 221 (92), 160 (100), 93 (47) and 77 (36) (Found: M^+, 313.08710. $C_{18}H_{16}ClNO_2$ requires M^+, 313.08695).

2-Anilino-7-bromo-non-2-ene-4,6-dione **6ah**. 32% (62% based on converted enaminone); oil; δ_H(200 MHz) appears as a 2.5:1 mixture of enol and keto tautomers; keto tautomer δ 1.00 (t, *J* 7.3, 3 H, *Me*CH_2CHBr), 1.99 (s, 3 H, Me), 2.08 (m, *J* 7.3, 2 H, MeC*H*$_2$CHBr), 3.76 (s, 2 H, CH_2), 4.17 (m, *J* 7.3, 1 H, $MeCH_2$C*H*Br), 5.19 (s, 1 H, CH=), 7.05–7.41 (m, 5 H, ArH) and 12.38 (br s, 1 H, NH); enol tautomer δ 1.00 (t, *J* 7.3, 3 H, *Me*CH_2CHBr), 2.01 (s, 3 H, Me), 2.08 (m, *J* 7.3, 2 H, MeC*H*$_2$CHBr), 4.17 (m, *J* 7.3, 1 H, $MeCH_2$C*H*Br), 4.93 (s, 1 H, CH=, 3-H or 5-H), 5.35 (s, 1 H, CH=, 5-H or 3-H), 7.05–7.41 (m, 6 H, ArH + OH) and 11.95 (br s, 1 H, NH); $\nu(CCl_4)$/cm^{-1} 1640 and 1593 (C=O); *m*/*z* (%) 325 (M^+ +2, 11), 323 (M^+, 10), 244 (18), 160 (100), 118 (37) and 77 (36) (Found: M^+, 323.05222. $C_{15}H_{18}BrNO_2$ requires M^+, 323.05213).

Cyclisation in Polyphosphoric Acid.—The reaction mixture arising from the dianions **3** and the esters **4** was quenched with water (10 mmol), and evaporated and then PPA (10-fold excess, w/w) added to the residue. The mixture was heated (70 °C) overnight and then neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 and the extract evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane–Et_2O–methanol, 10:10:1 as eluent) to isolate compounds **7** and **8**. Yields are reported in Table 1, physical data are reported below.

2-(4-Chlorophenyl)-6-methyl-1-phenylpyridin-4-one **7ab**. M.p. 235–237 °C; δ_H(200 MHz) 2.03 (s, 3 H, Me), 6.40 (br s, 1 H, 3-H or 5-H), 6.43 (br s, 1 H, 5-H or 3-H) and 7.00–7.40 (m, 9 H, ArH); $\nu(CCl_4)$/cm^{-1} 1628 (C=O); *m*/*z* (%) 297 (M^+ +2, 10), 295 (M^+, 38), 269 (39), 268 (28), 267 (100), 266 (38) and 77 (44) (Found: M^+, 295.07638. $C_{18}H_{14}ClNO$ requires M^+, 295.07639).

2-(4-Chlorophenyl)-6-methylpyran-4-one **8ab**. M.p. 110–112 °C (lit.,[9] 111–112 °C); δ_H(200 MHz) 2.41 (s, 3 H, Me), 6.26 (br s, 1 H, 3-H or 5-H), 6.76 (br s, 1 H, 5-H or 3-H), 7.49 (d, *J* 9, 2 H, ArH) and 7.73 (d, *J* 9, 2 H, ArH); $\nu(CCl_4)$/cm^{-1} 1625 (C=O); *m*/*z* (%) 222 (M^+ +2, 29), 192 (100) and 136 (67).

2,6-*Dimethyl*-1-*phenylpyridin*-4-*one* **7ac**. M.p. 196–198 °C (lit.,[6] 198 °C); δ_H(200 MHz) 1.85 (s, 6 H, Me), 6.25 (s, 2 H, 3-H and 5-H) and 7.16–7.51 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1637 (C=O); *m*/*z* (%) 199 (M^+, 45) and 170 (100).

2-*Ethyl*-6-*methyl*-1-*phenylpyridin*-4-*one* **7ad**. M.p. 172–174 °C; δ_H(200 MHz) 0.95 (t, *J* 7, 3 H, Me), 1.79 (s, 3 H, Me), 2.05 (q, *J* 7, 2 H, CH_2), 6.17 (br s, 1 H, 3-H or 5-H), 6.21 (br s, 1 H, 5-H or 3-H), 7.05–7.20 and 7.40–7.55 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1660 (C=O); *m*/*z* (%) 213 (M^+, 35), 185 (14), 170 (100) and 77 (22) (Found: M^+, 213.11478. $C_{14}H_{15}NO$ requires M^+, 213.11536).

2-*Methyl*-1-*phenyl*-6-*propylpyridin*-4-*one* **7ae**. M.p. 126–127 °C; δ_H(200 MHz) 0.69 [t, *J* 7, 3 H, $Me(CH_2)_2$], 1.36 (m, *J* 7, 2 H, $MeCH_2CH_2$), 1.78 (s, 3 H, Me), 2.00 (t, *J* 7, 2 H, $MeCH_2CH_2$), 6.17 (br s, 1 H, 3-H or 5-H), 6.19 (br s, 1 H, 5-H or 3-H), 7.05–7.20 and 7.40–7.55 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1635 (C=O); *m*/*z* (%) 227 (M^+, 46), 199 (12), 170 (100) and 77 (14) (Found: M^+, 227.13102. $C_{15}H_{17}NO$ requires M^+, 227.13101).

2-*Cyclopropyl*-6-*methyl*-1-*phenylpyridin*-4-*one* **7af**. M.p. 207–209 °C; δ_H(200 MHz) 0.60–1.00 (m, 5 H, aliphatic), 1.88 (s, 3 H, Me), 6.12 (d, *J* 2, 1 H, 3-H or 5-H), 6.30 (d, *J* 2, 1 H, 5-H or 3-H), 7.20–7.40 and 7.50–7.60 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1638 (C=O); *m*/*z* (%) 225 (M^+, 100), 197 (60), 196 (63), 182 (67), 170 (48) and 77 (53) (Found: M^+, 225.11526. $C_{15}H_{15}NO$ requires M^+, 225.11536).

2-*Cyclohexyl*-6-*methyl*-1-*phenylpyridin*-4-*one* **7ag**. M.p. 219–220 °C; δ_H(200 MHz) 0.70–1.80 (m, 11 H, aliphatic), 1.85 (s, 3 H, Me), 6.24 (br s, 1 H, 3-H or 5-H), 6.32 (br s, 1 H, 5-H or 3-H), 7.05–7.20 and 7.40–7.70 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1641 (C=O); *m*/*z* (%) 267 (M^+, 58), 239 (25), 212 (30), 196 (100), 170 (33) and 77 (40) (Found: M^+, 267.16170. $C_{18}H_{21}NO$ requires M^+, 267.16230).

2-*Ethyl*-6-*phenylpyran*-4-*one* **8ba**. M.p. 57–59 °C (lit.,[7] 58 °C); δ_H(200 MHz) 1.33 (t, *J* 7, 3 H, $MeCH_2$), 2.68 (q, *J* 7, 2 H, $MeCH_2$), 6.21 (br s, 1 H, 3-H or 5-H), 6.72 (br s, 1 H, 3-H or 5-H) and 7.49–7.80 (m, 5 H, ArH), $\nu(CCl_4)/cm^{-1}$ (C=O); *m*/*z* (%) 200 (M^+, 54) and 157 (100) (Found: M^+, 200.08395. $C_{13}H_{12}O_2$ requires M^+, 200.08372).

2-*Ethyl*-1-*isopropyl*-6-*methylpyridin*-4-*one* **7bc**. Oil; δ_H(200 MHz) 1.24 (t, *J* 7, 3 H, $MeCH_2$), 1.55 (d, *J* 7, 6 H, Me_2CH), 2.40 (s, 3 H, Me), 2.75 (q, *J* 7, 2 H, $MeCH_2$), 4.75 (sept, *J* 7, 1 H, Me_2CH), 6.19 (br s, 1 H, 3-H or 5-H) and 6.22 (br s, 1 H, 5-H or 3-H); $\nu(CCl_4)/cm^{-1}$ 1635 (C=O); *m*/*z* (%) 179 (M^+, 58), 151 (21), 136 (100) and 94 (73) (Found: M^+, 179.13100. $C_{11}H_{17}NO$ requires M^+, 179.13101).

2-*Ethyl*-6-*methylpyran*-4-*one* **8bc**. Oil; δ_H(200 MHz) 1.17 (t, *J* 7, 3 H, $MeCH_2$), 2.22 (s, 3 H, Me), 2.47 (q, *J* 7, 2 H, $MeCH_2$) and 6.01 (br s, 2 H, 3-H and 5-H); $\nu(CCl_4)/cm^{-1}$ 1664 (C=O); *m*/*z* (%) 138 (M^+, 65), 110 (11), 95 (100) and 69 (38) (Found: M^+, 138.06851. $C_8H_{10}O_2$ requires M^+, 138.06807).

2-*Ethyl*-1-*isopropyl*-6-*phenethylpyridin*-4-*one* **7cd**. Oil; δ_H(200 MHz) 1.30 (t, *J* 7.5, 3 H, $MeCH_2$), 1.59 (d, *J* 7, 6 H, Me_2CH), 2.66 (q, *J* 7.5, 2 H, $MeCH_2$), 2.99 (br s, 4 H, CH_2CH_2), 4.75 (sept, *J* 7, 1 H, Me_2CH), 6.30 (br s, 1 H, 3-H or 5-H), 6.34 (br s, 1 H, 5-H or 3-H) and 7.16–7.40 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1630 (C=O); *m*/*z* (%) 269 (M^+, 48), 226 (100), 150 (58), 123 (19) and 91 (18) (Found: M^+, 269.17797. $C_{18}H_{23}NO$ requires M^+, 269.17796).

2-*Ethyl*-6-*phenethylpyran*-4-*one* **8cd**. Oil; δ_H(200 MHz) 1.22 (t, *J* 7.5, 3 H, $MeCH_2$), 2.53 (q, *J* 7.5, 2 H, $MeCH_2$), 2.75–3.05 (m, 4 H, CH_2CH_2), 6.07 (br s, 1 H, 3-H or 5-H), 6.08 (br s, 1 H, 5-H or 3-H) and 7.16–7.40 (m, 5 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1667 (C=O); *m*/*z* (%) 228 (M^+, 20) and 91 (100) (Found: M^+, 228.11492. $C_{15}H_{16}O_2$ requires M^+, 228.11502).

Cyclisation with Gaseous Hydrogen Chloride.—Hydrogen chloride was bubbled into the reaction mixture arising from the dianions **3** and esters **4** during 2 h. The mixture was then neutralised with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 and the extract evaporated under reduced pressure. The residue was chromatographed on a silica gel column (hexane–Et_2O–methanol, 10:10:1 as eluent) to isolate compounds **7** and **8**. Yields are reported in Table 1, physical data are reported below.

Compounds **8ab**, **ba**, **bc** and **cd** were recognised by comparison with samples prepared as above.

2-*Methyl*-6-*phenylpyran*-4-*one* **8aa**. M.p. 85–86 °C (lit.,[7] 86 °C); δ_H(200 MHz) 2.41 (s, 3 H Me), 6.22 (br s, 1 H, 3-H or 5-H), 6.73 (d, *J* 0.5, 1 H, 5-H or 3-H), 7.52 (m, 3 H, ArH) and 7.79 (m, 2 H, ArH); $\nu(CCl_4)/cm^{-1}$ 1653 (C=O); *m*/*z* (%) 186 (M^+, 76) and 158 (100) (Found: M^+, 186.06795. $C_{12}H_{10}O_2$ requires M^+, 186.06807).

2-*Cyclohexyl*-6-*methylpyran*-4-*one* **8ag**. Oil; δ_H(200 MHz) 1.20–1.50, 1.65–2.00 and 2.20–2.40 (m, 11 H, aliphatic), 2.20 (s, 3 H, Me) and 6.00 (br s, 2 H, 3-H and 5-H); $\nu(CCl_4)/cm^{-1}$ 1664 (C=O); *m*/*z* (%) 192 (M^+, 100), 125 (80) and 85 (87) (Found: M^+, 192.11456. $C_{12}H_{16}O_2$ requires M^+, 192.11502).

Reaction of the γ-Dianion with Esters.—A THF solution of the appropriate ester **4** (7 mmol) was added to a cooled (−50 °C) solution of the γ-dianion **2** (5 mmol) and the mixture was stirred for 5 min under a nitrogen atmosphere. The solution was poured into saturated aqueous ammonium chloride and extracted with Et_2O. The organic layer was dried, evaporated under reduced pressure and the residue was chromatographed on silica gel (hexane–Et_2O, 1:1 as eluent). The reaction between the dianion **2d** and the ester **4a** was carried out under a variety of conditions: the temperature was varied from 0 to −50 °C; the dianion **2d** was prepared using various metallating agents; in one experiment the dianion solution was poured into the cooled ester solution. When a large excess of MeLi–TMEDA was used, 5-hydroxy-3-isopropylamino-1,5-diphenyl-hex-2-en-1-one **14** was recovered in 94% yield. The results are summarised in Table 2. Physical data are reported below.

3-(*Isopropylamino*)-1,5-*diphenylpent*-2-*en*-1,5-*dione* **12da**. M.p. 117–118 °C; δ_H(200 MHz) 1.30 (d, *J* 6, 6 H, Me), 3.68 (d sept, 1 H, CH), 4.04 (s, 2 H, CH_2), 5.61 (s, 1 H, CH=), 7.30–7.65 (m, 6 H, ArH), 7.75–8.10 (m, 4 H, ArH) and 11.57 (d, *J* 9, 1 H, NH); $\nu(CCl_4)/cm^{-1}$ 1607 and 1587 (C=O); *m*/*z* (%) 307 (M^+, 51) 202 (88), 160 (12), 105 (100) and 77 (57) (Found: M^+, 307.1576. $C_{20}H_{21}NO_2$ requires M^+, 307.15723).

5-*Hydroxy*-3,7-*bis*(*isopropylamino*)-1,5,9-*triphenylnon*-2,7-*diene*-1,9,*dione* **13da**. M.p. 107–108 °C (Found: C, 77.5; H, 7.5; N, 5.6. $C_{33}H_{38}N_2O_3$ requires C, 77.62; H, 7.50; N, 5.49%); δ_H(200 MHz) 1.00 (d, *J* 6, 6 H, Me), 1.03 (d, *J* 6, 6 H, Me), 2.88–3.23 (m, 4 H, CH_2), 3.40–3.53 (m, 3 H, CH + OH), 5.40 (s, 2 H, CH=) 7.20–7.94 (m, 15 H, ArH) and 11.67 (d, *J* 10, 2 H, NH); $\nu(CCl_4)/cm^{-1}$ 3407, 3314 (OH) and 1599 (C=O); *m*/*z* (%) 399 ($M^+-C_6H_9NO$, 2), 273 (31), 203 (54), 202 (44), 105 (100), 77 (47) and 58 (40) (Found: $M^+-C_6H_9NO$, 399.21964. $C_{27}H_{29}NO_2$ requires, M^+ 399.21983).

3-(*Isopropylamino*)-1-*phenylhex*-2-*ene*-1,5-*dione* **12dc**. Oil; δ_H(60 MHz) 1.30 (d, *J* 6, 6 H, Me), 2.28 (s, 3 H, Me), 3.47 (s, 2 H, CH_2), 3.68 (d sept, 1 H, CH), 5.67 (s, 1 H, CH=), 7.37–7.67 (m, 3 H, ArH), 7.83–8.10 (m, 2 H, ArH) and 11.50 (d, *J* 9, 1 H, NH); $\nu(CCl_4)/cm^{-1}$ 1718 and 1587 (C=O); *m*/*z* (%) 245 (M^+, 59), 228 (14), 212 (21), 202 (63), 140 (34), 105 (100) and 77 (31) (Found: M^+, 245.14163. $C_{15}H_{19}NO_2$ requres M^+, 245.14157).

5-*Hydroxy*-3,7-*bis*(*isopropylamino*)-5-*methyl*-1,9-*diphenylnona*-2,7-*diene*-1,9-*dione* **13dc**. M.p. 79–81 °C (Found: C, 75.1; H, 8.2; N, 6.4. $C_{28}H_{36}N_2O_3$ requires C, 74.97; H, 8.09; N, 6.24%); δ_H(200 MHz) 1.22 (d, *J* 6, 12 H, Me), 1.41 (s, 3 H, Me), 2.53–2.80 (AB, J_{AB} 14, 4 H, CH_2), 4.04 (m, 3 H, CH + OH), 5.63 (s, 2 H, CH=) 7.26–7.50 (m, 6 H, ArH), 7.76–7.94 (m, 4 H, ArH) and 11.66 (d, *J* 9, 2 H, NH); $\nu(CCl_4)/cm^{-1}$ 3407, 3307 (OH) and 1601 (C=O); *m*/*z* (%) 448 (M^+, 1), 267 (5), 245 (24), 203 (40), 202 (33), 105 (100) and 77 (49) (Found: M^+, 448.27263. $C_{28}H_{36}N_2O_3$ requires M^+, 448.27257).

3-(*Isopropylamino*)-1-*phenyloct*-2-*ene*-1,5-*dione* **12de**. Oil; δ_H(60 MHz) 0.89 [t, *J* 7, 3 H, *Me*$(CH_2)_2$], 1.26 (d, *J* 6, 6 H, Me), 1.26–1.90 (m, 2 H, MeCH_2CH_2), 2.50 (t, *J* 7, 2 H, MeCH_2CH_2), 3.38 (s, 2 H, CH_2), 3.38–3.90 (d sept, 1 H, CH), 5.53 (s, 1 H, CH=), 7.23–7.53 (m, 3 H, ArH), 7.67–7.97 (m, 2 H, ArH) and 11.33 (d, *J* 10, 1 H, NH); $\nu(CCl_4)/cm^{-1}$ 1717 and 1606 (C=O); *m*/*z* (%) 273 (M^+, 10), 255 (63), 240 (100), 202 (11), 105 (17) and 77 (7) (Found: M^+, 273.17288. $C_{17}H_{23}NO_2$ requires M^+, 273.17287).

5-*Hydroxy*-3,7-*bis*-(*isopropylamino*)-1,9-*diphenyl*-5-*propyl*-*nona*-2,7-*diene*-1,9-*dione* **13de**. M.p. 88–89 °C (Found: C, 75.4; H, 8.4; N, 6.0. $C_{30}H_{40}N_2O_3$ requires C, 75.59; H, 8.46; N, 5.88%); δ_H(200 MHz) 1.02 [t, *J* 9, 3 H, *Me*$(CH_2)_2$], 1.23 (d, *J* 6 H, Me), 1.29 (d, *J* 5, 6 H, Me), 1.47–1.67 (m, 2 H, MeCH_2CH_2), 1.67–1.80 (m, 2 H, MeCH_2CH_2), 2.59–2.76 (AB, J_{AB} 12, 4 H, CH_2), 3.80 (br s, 1 H, OH), 4.04 (m, 2 H, CH), 5.63 (s, 2 H, CH=), 7.30–7.51 (m, 6 H, ArH), 7.77–7.92 (m, 4 H, ArH) and 11.64 (d, *J* 9, 2 H, NH); $\nu(CCl_4)/cm^{-1}$ 3405, 3290 (OH) and 1598 (C=O); *m*/*z* (%) 476 (M^+, 1) 295 (2), 273 (27), 202 (37), 105 (100) and 77 (48) (Found: M^+, 476.30389. $C_{30}H_{40}N_2O_3$ requires M^+, 476.30387).

5-*Hydroxy*-3-(*isopropylamino*)-1,5-*diphenylhex*-2-*en*-1-*one* **14**. M.p. 50–51 °C; δ_H(200 MHz) 1.11 (d, *J* 6, 3 H, Me), 1.17 (d, *J* 6, 3 H, Me), 1.73 (s, 3 H, Me), 2.76 (s, 2 H, CH_2), 3.62–3.80 (m, 1 H, CH), 3.90 (br s, 1 H, OH), 5.47 (s, 1 H, CH=), 7.30–7.80 (m, 10 H, ArH) and 11.53 (d, *J* 7, 1 H, NH); $\nu(CCl_4)/cm^{-1}$ 3437 (OH) and 1598 (C=O); *m*/*z* (%) 323 (M^+, 10), 280 (8), 238 (2), 203 (46), 105 (100), 98 (27) and 77 (91) (Found: M^+, 323.18868. $C_{21}H_{25}NO_2$ requires M^+, 323.18852).

3-(*Methylamino*)-1-*phenylhept*-2-*ene*-1,5-*dione* **12fd**. Oil; δ_H(60 MHz) 1.07 (t, *J* 7.3, 3 H, *Me*CH_2), 2.57 (q, *J* 7.2, 2 H, MeCH_2), 2.96 (d, *J* 5.3, 3 H, NMe), 3.42 (s, 2 H, CH_2), 5.66 (s, 1 H, CH=), 7.30–7.55 (m, 3 H, ArH), 7.75–7.97 (m, 2 H, ArH) and 11.30 (br s, 1 H, NH); $\nu(CCl_4)/cm^{-1}$ 1719 and 1609 (C=O); *m*/*z* (%) 231 (M^+, 34), 214 (20), 202 (93), 174 (100), 105 (92) and 77 (45) (Found: M^+, 231.12610. $C_{14}H_{17}NO_2$ requires M^+, 231.12592).

5-*Ethyl*-5-*hydroxy*-3,7-*bis*(*methylamino*)-1,9-*diphenylnona*-2,7-*diene*-1,9-*dione* **13fd**. Oil (Found: C, 73.95; H, 7.4; N, 6.7. $C_{25}H_{30}N_2O_3$ requires C, 73.86; H, 7.44; N, 6.89%); δ_H(200 MHz) 1.06 (t, *J* 5, 3 H, *Me*CH_2), 1.78 (q, *J* 5, 2 H, MeCH_2), 2.73 (AB, J_{AB} 14, 4 H, CH_2), 2.74 (br s, 1 H, OH), 3.05 (d, *J* 5, 6 H, Me), 5.67 (s, 2 H, CH=), 7.30–7.50 (m, 6 H, ArH), 7.80–7.90 (m, 4 H, ArH) and 11.60 (br s, 2 H, NH); $\nu(CCl_4)/cm^{-1}$ 3300 (OH) and 1606 (C=O); *m*/*z* (%) 406 (M^+, 1), 232 (22), 174 (40), 105 (100) and 77 (50) (Found: M^+, 406.22575. $C_{25}H_{30}N_2O_3$ requires M^+, 406.22563).

References

1 G. Bartoli, M. Bosco, R. Dalpozzo, M. Guerra, C. Cimarelli and G. Palmieri, *J. Chem. Soc., Perkin Trans. 2*, 1992, 649.
2 G. Bartoli, M. Bosco, R. Dalpozzo, C. Cimarelli and G. Palmieri, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2095.
3 G. Bartoli, M. Bosco, C. Cimarelli, R. Dalpozzo, G. De Munno, G. Guercio and G. Palmieri, *J. Org. Chem.*, 1992, **57**, 6020.
4 G. Bartoli, M. Bosco, C. Cimarelli, R. Dalpozzo and G. Palmieri, *Tetrahedron*, 1993, **49**, 2521.
5 S. Boatman, R. E. Smith, G. F. Morris, W. G. Kofron and C. R. Hauser, *J. Org. Chem.*, 1967, **32**, 3817.
6 S. Hünig and G. Köbrich, *Liebigs Ann. Chem.*, 1958, **617**, 181; G. Jones, *Pyridines and their Benzo Derivatives: Synthesis*, in *Comprehensive Heterocyclic Chemistry*, eds. A. J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984, **2**, 499.
7 S. D. Work and C. R. Hauser, *J. Org. Chem.*, 1963, **28**, 725.
8 R. F. Abdulla, T. L. Emmick and H. M. Taylor, *Synth. Commun.*, 1977, **7**, 305; R. F. Abdulla, K. H. Fuhr and H. M. Taylor, *Synth. Commun.*, 1977, **7**, 313.
9 R. J. Light and C. R. Hauser, *J. Org. Chem.*, 1960, **25**, 538.
10 C. Uncuta, T. S. Balaban, A. Petride, F. Chiraleu and A. T. Balaban, *Rev. Roum. Chim.*, 1989, **34**, 1425.
11 S. Boatman and C. R. Hauser, *J. Org. Chem.*, 1966, **31**, 1785.
12 R. V. Singh and J. P. Tandon, *J. Prakt. Chem.*, 1979, **321**, 151.

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