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THE REACTION OF α-DIKETONES WITH PRIMARY HETEROAROMATIC AMINES. SYNTHESIS AND REACTIONS OF IMIDAZO[1,2-α]PYRIDIN-3(2*H*)-ONES AND *N*-HETEROARYL α-IMINOKETONES

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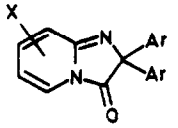
Abstract. The reaction of α-diketones with various primary heteroaromatic amines including pyridine, diazine, and azole derivatives has been studied. Benzils react with 2-aminopyridines to give 2,2-diarylimidazo[1,2-α]pyridin-3(2*H*)-ones 1 as stable products, in good yields. With the other aminoheterocycles only *N*-heteroaryl-α-iminoketones 4 are obtained when the reaction takes place. On the contrary, biacetyl and 1-phenyl-1,2-propanedione react only with 2-aminopyridine to afford an unidentified biacetyl self-condensation product and the α-ketoaminal 5, respectively. In addition, some new reactions of compounds 1 with retention or not of the bicyclic structure are reported.

Introduction

In connection with our interest in the condensation reactions of α-dicarbonyl compounds with primary amines[1] and as a part of a research project focussed on the synthesis and reactivity of α-iminoketones and related bifunctional electrophiles,[2] we explored the reaction of simple α-diketones with primary heteroaromatic amines including pyridine, diazine and azole derivatives. Previous work in this field has been mainly concerned with reactions of phenylglyoxal and related glyoxals in acidic medium.[3] Recently we have also described the reaction between arylglyoxals and aminopyridines in neutral medium.[4]

To the best of our knowledge the only reaction between an α-diketone and an aminoheterocycle was reported by Sokov, who described the synthesis of aminoacid **2a** upon heating benzil with 2-aminopyridine at 165-225°C.[5] He claimed that the first reaction product was a diol which changed into 2,2-diphenylimidazo[1,2-α]pyridin-3(2*H*)-one **1a** (X = H, Ar = Ph) through a pinacol-pinacolone type rearrangement. According to Sokov, **1a** is a very unstable and not isolable product that is hydrolyzed very easily to yield **2a**, the only isolated product in his case. We have recently shown that Sokov's proposal was correct although **1a** can be isolated as a stable compound.[6] We now report that compounds **1** can be synthetised very easily by working under Lewis acid catalysis in anhydrous medium. This simple experimental modification allowed for the preparation of series of compounds **1** as perfectly stable products. Compounds of the imidazo[1,2-α]pyridin-3-one type have seldom been described so far. Dehydration of *N*-(2-pyridyl)glycine has been previously reported to yield **3** which proved to be unstable in water or alcohol.[7] Besides this work nothing is known about the chemistry of compound **3** probably due to its limited availability and instability,

decomposing spontaneously on standing at room temperature.[8] In order to gain some insight into the chemical behavior of compounds 1 we investigated their reaction with various O- and *N*-nucleophiles, their reduction with complex metal hydrides and their catalytic hydrogenation.



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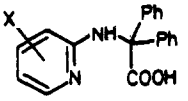

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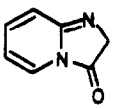

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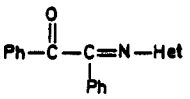

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We also studied the reaction of benzil with other related aminoheterocycles, leading to novel *N*-heteroaryl α-iminoketones 4. Moreover, the reaction of other α-diketones such as diacetyl and 1-phenyl-1,2-propanedione is described.

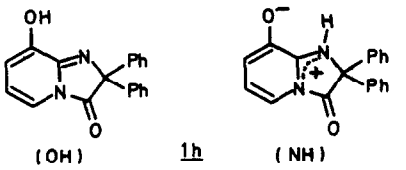
Results and discussion

Reactions of benzils with C-substituted 2-aminopyridines. Synthesis of 2,2-diaryl-imidazo[1,2-a]pyridin-3(2H)-ones, 1. The reaction of an equimolar amount of benzil or its derivatives with 2-aminopyridine or its C-substituted derivatives in refluxing xylene with a water separator and in the presence of $ZnCl_2$/α-phenylethylamine complex as catalyst, afforded compounds 1 as crystalline products (with the exception of 1j) in good yields (see Experimental, Table 1).

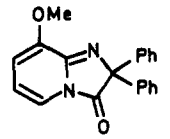
The structure of these products was established by their analytical and spectroscopic data. Thus, the IR spectra of compounds 1 displayed the C=O and C=N absoption (except for compound 1h, whose structure is discussed below) in the range 1750-1720 cm^{-1} and 1650-1630 cm^{-1}, respectively (see Table 1). Table 2 shows the ^{1}H-NMR spectral data for compounds 1a-e. As expected, the most deshielded signal corresponds to H-5 (7.04 - 7.25 ppm) and the most shielded signal to H-6 (5.53 - 5.92 ppm). The coupling constants are generally in good agreement with those observed for aromatic imidazo[1,2-a]pyridines.[9] Table 3 shows the ^{13}C-NMR chemical shifts of the various imidazopyridones 1 prepared. The most significant resonances are those due to benzhydryl (C-2, δ 76.5 - 78.6), carbonyl (C-3, δ 181.9 - 178.1) and amidine carbons (C-9, δ 157.3 - 151.9). Compound 1h is again an exception, and the signals corresponding to the above mentioned carbons are considerably shielded.
As previously described by us,[6] the structure of compounds 1 was conclusively proven by X-ray diffraction study carried out for compound 1a.

Two tautomeric forms, hydroxy (OH) and meso-ionic (NH) are possible for compound 1h, obtained from benzil and 2-amino-3-hydroxypyridine. Compounds 1g and 1a-HCl may be considered as spectral models for the OH and NH tautomers, respectively. Comparison of spectral data (IR, ^{13}C-NMR, and UV) of 1h with those of the model system (see Tables 1 and

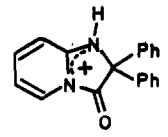
3) clearly shows that the meso-ionic tautomer is predominant in neutral medium. Thus the carbonyl absorption in the IR spectrum of 1h appears 40 cm^{-1} higher than that of the methoxy derivative 1g; this is similar to the shift observed for compound 1a-HCl with respect to 1a, albeit quantitatively smaller. The ^{13}C-NMR data for the imidazolone nucleus are equally illustrative, all of them show a strong shielding for compound 1h relative to those of hydroxy model (compound 1g). A similar effect is observed mainly for the benzhydryl (C-2) and amidine (C-9) carbons between compounds 1a-HCl and 1a. The UV data are conclusive for structural assignment. Thus the UV spectrum in methanol of compound 1h was compared (Figure) with those of 1a, 1a-HCl, and 1g. This comparison showed that the compound is not in the hydroxy form and should have the meso-ionic structure. The presence of a positive charge delocalized over both nitrogen atoms must be, consequently, reponsible for the observed spectral effects. Thus, compound 1h must exist principally as 2,2-diphenyl-3-oxo--1*H*-imidazo[1,2-α]pyridinium-8-olate (NH) tautomer both in the solid state and in solution. Very recently, Sliwa and coworkers[10] have studied the tautomerism in aqueous solution of the 8-hydroxyimidazo-[1,2-α]pyridine and demonstrated the predominance of the dipolar form in neutral medium.



1h



1g



1a(HCl)

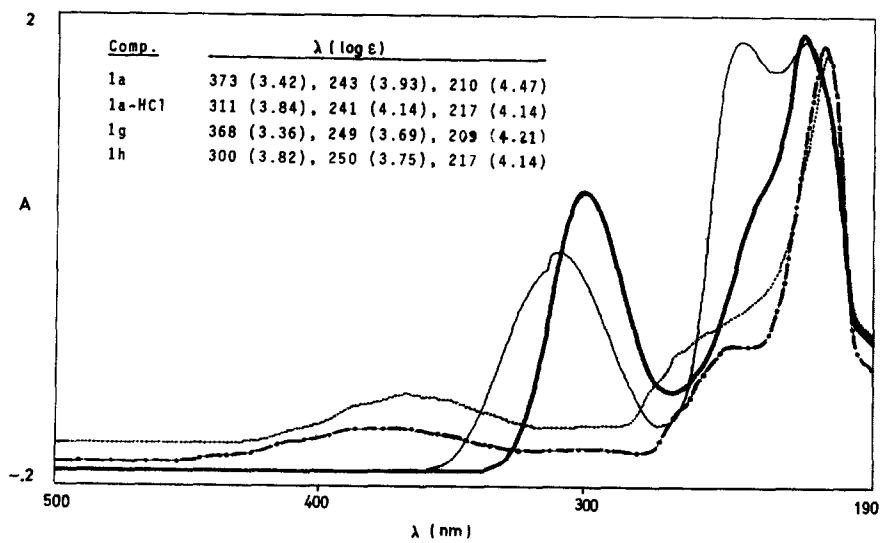
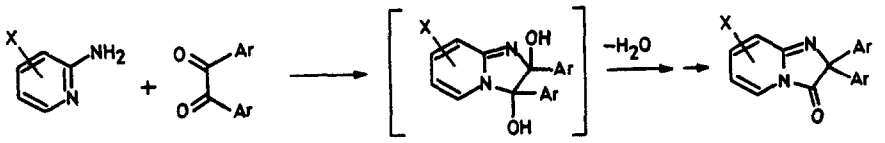


Figure.- UV spectra in methanol of compounds 1a (····), 1a-HCl (—), 1g (—·—), and 1h (—).

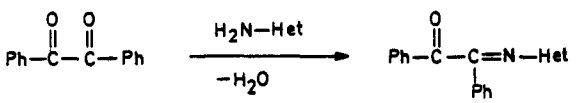
The isolation and characterization of imidazo[1,2-a]pyridones **1** as stable compounds and their independent transformation into the corresponding acids **2** (see below) support the reaction course proposed by Sokov[5a] for the formation of aminoacid **2a** by the reaction of benzil with 2-aminopyridine. Therefore, the reaction of 2-aminopyridines with benzil and derivatives gave the corresponding intermediary dihydroxyimidazolines which underwent a pinacol-pinacolone type rearrangement under the reaction conditions to produce compounds **1** (Scheme 1). The products **1** are stable, but react readily with water and a variety of nucleophiles to yield various derivatives of acid **2a**. The data for these reactions clearly indicate that the formation of the intermediary dihydroxyimidazoline is the rate-determining step. For example, when the reaction times measured for the formation of **1a**, **1i** and **1j** as well as those for **1a**, **1c** and **1f** (Table 1) are compared, just electronic factors are found to be relevant. The reaction between benzil and 2-amino-5-nitropyridine does not occur, even after prolonged reaction times. The reaction apparently proceeds faster with an increasing basicity of the 2-aminopyridine and with an increasing electrophilicity of the dicarbonyl compound.



1

Scheme 1

Reaction of benzyl with other aminoheterocycles. The reactions of benzil with 3- and 4-amino-pyridines, 3-aminopyrazole and 2-aminothiazole under experimental conditions similar to those used for 2-aminopyridines afforded the corresponding α-iminoketones **4** as stable crystalline compounds (Scheme 2). However, no reaction occurred with 2-aminopyrazine, 2-aminopyrimidine and 2-aminobenzimidazole, the starting materials being recovered. The use of stronger reaction conditions and of different catalyst ($ZnCl_2$, $AlCl_3$, $TiCl_4$, etc) was also fruitless.



4

4	Het	Yield (%)
a	3-Pyridyl	65
b	4-Pyridyl	20
c	3(5)-Pyrazolyl	15
d	2-Thiazolyl	60

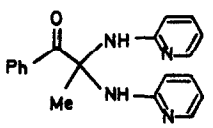
Scheme 2

It is very significant that such a marked difference of reactivities was observed between 2-aminopyridine and the other 2-aminoheterocycles studied in their reactions with benzils. Although this finding could be accounted for in terms of the basicity of the amino group and the electronic character of the heteroaromatic ring, it is difficult at present to rationalize satisfactorily the dependence of the reaction pattern on the nature of the heteroaromatic amine.

Reactions of other α-diketones. The reactions with diacetyl and 1-phenyl-1,2-propanedione were tried under similar conditions to those described for the synthesis of their corresponding monoimines with anilines.[11] It was found that the reaction proceeded only with 2-aminopyridines, the reaction of the other heteroaromatic amines resulting in the recovery of the starting materials or the formation of intractable mixtures.

Treatment of 2-aminopyridine with biacetyl at room temperature, with or without solvent (ether or benzene), gave a viscous yellow-orange oil. This product is homogeneous (tlc) but does not contain the 2-aminopyridine moiety, and must be an autocondensation polymer of biacetyl, whose structure and composition have not been determined yet. However, the spectral properties of the product do not agree with either of the known biacetyl self-condensation products.[12] Attempts to establish the structure of this compound are now in progress.

A similar reaction between 1-phenyl-1,2-propanedione and 2-aminopyridine yielded aminal 5 as the sole product. The best result (54 %) was realized when the reaction was carried out in refluxing ether with equimolar amounts of reagents. The exclusive formation of 5 should be a consequence of the higher reactivity of the aliphatic carbonyl than the aromatic one.

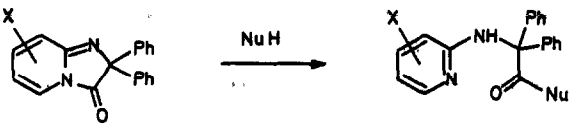


5

It is difficult to completely understand what the driving forces are for formation of the observed products in the reactions above mentioned. The large number of variables coupled with differences in reaction conditions make speculation hazardous.

Reactions of compounds 1. Treatment of compounds 1 (Ar = Ph) with some oxygen nucleophiles (water and primary alcohols) and nitrogen nucleophiles (primary amines and hydrazine) afforded *N*-(2-pyridyl)aminodiphenylacetic acid **2a** and its derivatives **6-8** in good to excellent yields (Scheme 3 and Table 4). The reaction was carried out under solvolytic conditions, generally in a refluxing nucleophilic solvent, and in some cases in the presence of an inert co-solvent. However, the reaction failed with more hindered nucleophiles such as 2-propanol, *tert*-butanol, *tert*-butylamine and α-phenylethylamine. Compounds 1 substituted in the position 8 with Me, OMe, and OH groups resisted this type of reaction even on prolonged heating.

The nucleophile initially adds to the carbonyl group to yield the intermediate 9, and the aromatization of its pyridine ring appears to be the driving force for the reaction.

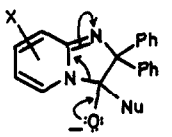


1	X
a	H
b	5-Me
c	6-Me
d	7-Me
e	6-Cl

	Nu
2	OH
6	OR
7	NHR
8	$NHNH_2$

Scheme 3

This interpretation is supported by the fact that compound 10a, readily obtained by catalytic hydrogenation of 1a (see below), is inert to the same nucleophiles.



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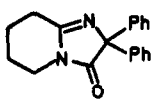


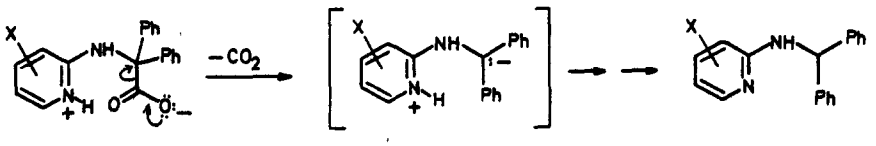
10

a: X = H

b: X = Me

The inertness of bulkier nucleophiles might be ascribed to the steric hindrance to the formation of 9. On the other hand, the lack of reactivity of nucleophiles towards 8-substituted imidazo[1,2-a]pyridin-3-ones cannot be rationalized at present.

In the reaction of compounds 1 with water the corresponding amines 11 were formed in addition to aminoacids 2 in various ratios depending upon the reaction time. Compounds 2 were the main product in short time reactions (<3h), while the amines 11 predominated on prolonged heating. Scheme 4 shows a possible reaction pathway for the decarboxylation of the dipolar structure of the aminoacids 2.

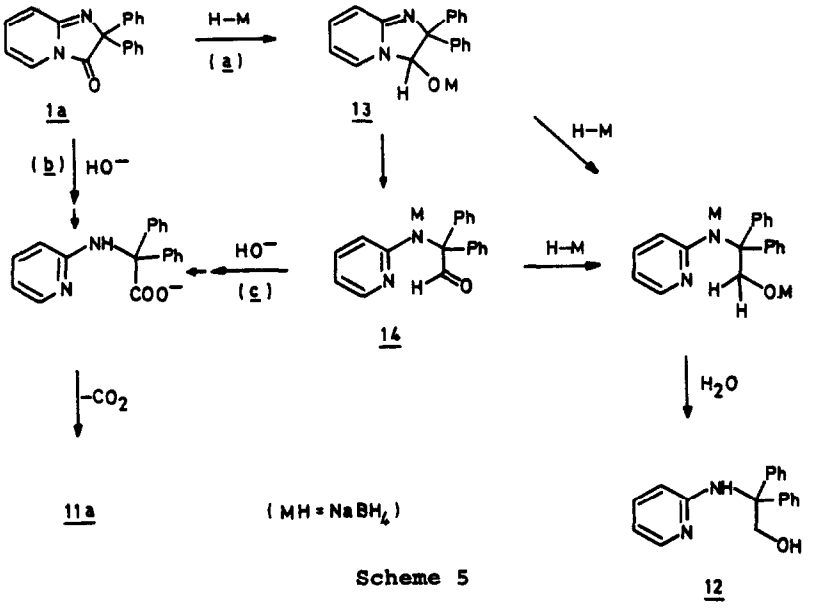


2 11

(a: X = H; b: X = 4-Me)

Scheme 4

Compound 1a reacts with complex metal hydrides in different fashion depending on the nature of the reagent. The reaction of 1a with sodium borohydride in boiling 2-propanol afforded aminoalcohol 12[13] (70 %) together with variable amounts of the sodium salt of aminoacid 2a and amine 11a depending on the reaction time. It is clear that amine 11a arises

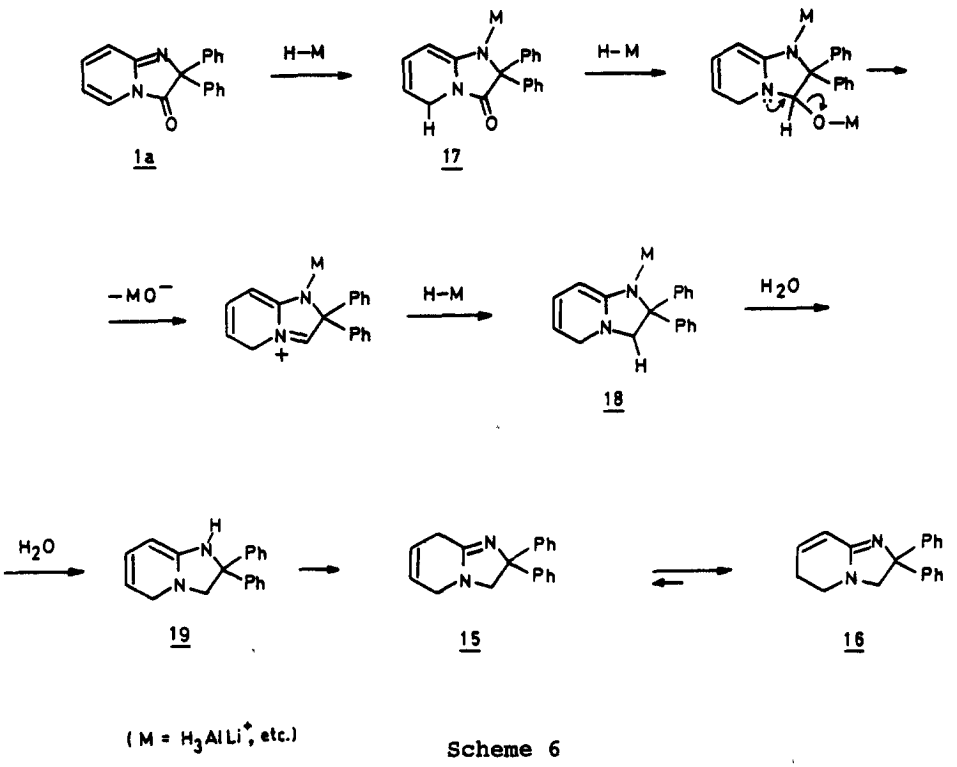


Scheme 5

from the decarboxylation of the sodium salt of 2a. Formation of aminoalcohol 12 may be initiated by addition of the hydride to the carbonyl group to yield the corresponding alkoxide 13 (analogous to 9) (Scheme 5). Transformation of 13 to 12 can be rationalised by the direct reductive opening of the imidazoline ring or by the ring opening to aminoaldehyde 14, in a similar fashion to reactions with O- and *N*-nucleophiles, followed by its reduction to 12. As for the formation of aminoacid 2a, a more likely route should be the imidazolone ring opening of 1a with sodium hydroxide (route b) present in commercial sodium borohydride,[14] although the alternative route involving a Cannizzaro reaction (route c) is not ruled out.

The reaction of 1a with a freshly prepared ether solution of $LiAlH_4$[15] gave a bicyclic amidine 15 as the main product. Isomerization of 15 to the more stable conjugated amidine 16 was easily achieved in quantitative yield by heating a solution of 15 in different solvents and also by column chromatography on silica gel. Formation of compound 15 can be explained by a 1,6-reduction of the 1-azatrienic moiety of 1a to 17 followed by reduction of the carbonyl group in the intermediate 17 to give 18, which finally affords amidine 15 after quenching and kinetic isomerization of the resulting dienamine 19 (Scheme 6).

The fact that the reaction takes place with retention of the bicyclic structure clearly indicates that the 1-azatrienic system must be reduced first; prior reduction of the carbonyl group should result in imidazoline ring opening as in the reaction with $NaBH_4$. Evidently **1a** has an ambident electrophilic character, carbons 3 and 5 being electrophilic centers. The different *site*-selectivity observed for both reagents suggests that carbon 3 (carbonyl group) is the softer center (attacked by $NaBH_4$, a softer reducing agent) and carbon 5 is the harder one (attacked by $LiAlH_4$, a harder reducing agent).[16]



Scheme 6

Reduction of the pyridine ring in compounds **1** was easily achieved by catalytic hydrogenation in ethyl acetate at room temperature over 10 % palladium-charcoal to give compounds **10** as the sole product in excellent yields. This result is closely related to that observed in the catalytic hydrogenation of aromatic imidazo[1,2-a]pyridines giving aromatic imidazole derivatives. In our case a similar reduction yielded cyclic *N*-acylamidines of known inertness in catalytic hydrogenation.[17]

Experimental

Melting points were determined in a Büchi 510 apparatus and are uncorrected. IR spectra vere recorded with a Perkin-Elmer 257 grating spectrophotometer, υ values in cm^{-1}. ^1H NMR spectra were recorded with a Varian T-60A (60 MHz), or with a Bruker AM-300 (300 MHz), using TMS as internal standard. ^{13}C NMR spectra were recorded with a Varian FT-80 (20.15 MHz). ^1H and ^{13}C chemical shifts are reported in δ units downfield from TMS. Mass spectra were determined with a Varian MAT 711 apparatus (electron impact). Elemental analyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C, Barcelona (Spain). Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column and analytical tlc, respectively. Aminoheterocycles and α-dicarbonyl compounds were available through commercial sources, except *2-amino-3-methoxypyridine* which was obtained by methylation of commercial 2-amino-3-hydroxypyridine with ethereal diazomethane prepared *in situ* from Diazald ; mp 82-83 °C (Lit.[18] 79-79.5 °C). *p,p'-Dinitrobenzil* was prepared by the method of Chattaway and Coulson[19]. *1-Phenyl-1,2-propanedione* was obtained by acid hydrolysis of commercial isonitrosopropiophenone.[20]

Synthesis of 2,2-diarylimidazo[1,2-a]pyridin-3(2*H*)-ones 1 from benzils and 2-aminopyridines. General Procedure.- In a flask equipped with a Dean-Stark device for azeotropic distillation of water and a reflux condenser, the amine (9.3 mmol) and an equimolar amount of the benzil were dissolved in anhydrous xylene (30 ml), and a trace of catalyst (α-phenylethylamine/$ZnCl_2$ complex) was added. Enough xylene was added into the Dean-Stark device to avoid loss of solvent from the reaction mixture. Reflux was continued for the time indicated in each case. The warm reaction mixture was filtered, the solvent distilled off *in vacuo*, and the resultant crude product, solid or viscous oil, was purified by recrystallization from a suitable solvent or by flash column chromatography on silica gel using benzene/ethyl acetate mixtures as eluent. Compounds 1 were yellow crystals except 1i (brown crystals), 1h (white crystals), and 1j (viscous yellow oil). Reaction conditions, yields, physical and spectroscopic data for compounds 1 are shown in Tables 1, 2 and 3.

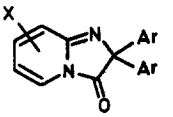
2,2-Diphenyl-3-oxoimidazo[1,2-a]pyridinium Chloride, 1a-HCl. To a suspension of 1a (0.5 g) in water (2 ml), concentrated hydrochloric acid (12N, 1ml) was added. The initial yellow color faded quickly and a white solid was formed. This solid was disgregated with water and filtered. A nearly quantitative yield (0.59 g) of 1a-HCl was obtained, mp 148-150 °C (THF). IR (KBr): υ 3500, 2500, 1800, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{15}ClN_2O$: C, 70.7; H, 4.6; Cl, 11.0; N, 8.7. Found: C, 70.5; H, 4.5; Cl, 10.8; N, 8.6.

Synthesis of *N*-heteroaryl α-iminoketones 4 from benzil and aminoheterocycles. A similar general procedure to that for compounds 1 was followed, with the only difference that a variable volume of xylene was used depending on the amine.
1-Benzoyl-1-phenyl-N-(3-pyridyl)methanimine (4a). This compound was prepared from benzil (2.0 g, 9.5 mmol) and 3-aminopyridine (0.89 g, 9.5 mmol) in xylene (15 ml). Reaction time, 48 h. The pure iminoketone 4a was obtained by crystallization from ethanol as a yellow crystalline solid (65 %), mp 97-98 °C. IR (KBr) υ 1665 (C=O), 1605 (C=N) cm^{-1}. ^{13}C-NMR ($DCCl_3$) δ 196.1 (C=O), 168.0 (C=N). Ms m/z 286 (M^+, 19 %), 181 (M^+-PhCO, 100). Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.7; H, 4.9; N, 9.8. Found: C, 80.0; H, 5.0; N, 9.8.
1-Benzoyl-1-phenyl-N-(4-pyridyl)methanimine (4b). This compound was obtained from benzil (2.23 g, 10.6 mmol) and 4-aminopyridine (1.0 g, 10.6 mmol) in xylene (15 ml). Reaction time, 50 h. The crude yellow viscous oil was crystallized from ethanol to separate unaltered benzil (0.65 g). The remaining crude product was chromatographied on silica gel using benzene/ethyl acetate (1:1) as eluent, and the product was recrystallized from ethanol as pale yellow crystals (20 %), mp 90-91 °C. IR (KBr).υ.1670 (C=O), 1630 (C=N) cm^{-1}. ^{13}C-NMR ($DCCl_3$) δ 194.9 (C=O), 167.2 (C=N). Ms m/z 286 (M^+, 6 %), 181 (M^+-PhCO, 100). Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.7; H, 4.9; N, 9.8. Found: C, 80.0; H, 4.8; N, 9.8.

1-Benzoyl-1-phenyl-N-[3(5)-pyrazolyl]methanimine (4c). This compound was prepared from benzil (0.65 g, 3.1 mmol) and 3(5)-aminopyrazole (0.25 g, 3.1 mmol) in xylene (5 ml). Reaction time, 6.5 h. The yellow viscous oil obtained was chromatographed on silica-gel using benzene/ethyl acetate (10:1) as eluent, and the product was recrystallized from methanol as yellow crystals (15 %), mp 144-146 °C. IR (KBr) υ 3310 (NH), 1660 (C=O), 1590,

Table 1

Synthesis and relevant IR data of compounds 1



Comp.	Ar	X	t(h)	Yield (%)	Mp (°C)	υ (cm⁻¹) C=O	υ (cm⁻¹) C=N
1a	Ph	H	7	70	116	1750	1650
1b	Ph	5-Me	5	75	146	1750 1730	1650
1c	Ph	6-Me	6	70	106-108	1730	1650
1d	Ph	7-Me	3	85	158-160	1740 1720	1650
1e	Ph	8-Me	5	75	165-166	1730	1640
1f	Ph	6-Cl	24	70	102	1740	1640
1g	Ph	8-OMe	26	75	184-186	1740	1640
1h	Ph	8-OH	22	60	220-223	1780	
1i	p-$NO_2C_6H_4$	H	1	70	190-192	1730	1650
1j	p-$MeOC_6H_4$	H	9	41	oil	1745	1655

a) Reaction progress was monitored by tlc. Longer reaction times cause, in some cases, formation of by-products as well as considerably lower yields. b) In pure, isolated, product recrystallized from ethyl acetate except **1f** (ethyl acetate/hexane), **1g** (benzene) and **1i** (toluene). Compound **1j** was purified by flash chromatography. All compounds gave satisfactory microanalyses. c) In KBr pellet except **1j** ($HCCl_3$).

1570, 1400 cm^{-1}. ^{13}C-NMR ($DCCl_3$) δ 199.1 (C=O), 165.1 (C=N). Ms m/z 275 (M^+, 18 %), 170 (M^+-PhCO, 100). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.1; H, 4.7; N, 15.3. Found: C, 73.9; H, 4.9; N, 15.0.

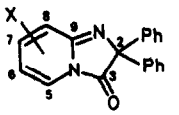
1-Benzoyl-1-phenyl-N-(2-thiazolyl)methanimine (**4d**). This compound was obtained from benzil (1.0 g, 4.8 mmol) and 2-aminothiazole (0.47 g, 4.8 mmol) in xylene (20 ml). Reaction time, 6.5 h. Pure iminoketone **4d** was obtained by crystallization of crude product from methanol as yellow crystals (60 %), mp 108-110 °C. IR (KBr) υ 1665 (C=O), 1630 (C=N) cm^{-1}. ^{13}C-NMR ($DCCl_3$) δ 197.0 (C=O), 168.8 (C=N). Ms m/z 210 (9 %), 179 (4), 105 (PhCO, 100). Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.8; H, 4.1; N, 9.6; S, 10.9. Found: C, 69.8; H, 4.4; N, 9.6; S, 11.0.

Synthesis of 1-phenyl-2,2-bis(2-pyridylamino)-1-propanone (5). A mixture of 1-phenyl-1,2-propanedione (0.5 g, 3.4 mmol) and 2-aminopyridine (0.64 g, 6.8 mmol) in ether (15 ml) was refluxed for 24 h, after which time a white solid precipitated. This solid was filtered and washed whith cold ether, affording 0.6 g (54 %) of the oxo-aminal **5**, which was characterized without further purification. Mp 130-132 °C. IR (KBr) υ 3400 (sharp, NH), 3240 (broad, NH), 1710 (C=O), 1605, 1570. ^1H-NMR (DMSO-d_6, 60 MHz) δ 2.2 (s, 3H, Me), 6.2-8.2 (m, 13H, aromatics). ^{13}C-NMR (DMSO-d_6) δ 200.0 (C=N), 76.2 (NCN). Ms m/z 318 (M^+, 8 %), 181 (98), 105 (PhCO, 89), 78 (C_5H_4N, 100). Anal. Calcd for $C_{19}H_{18}N_4O$: C, 71.7; H, 5.7; N, 20.1. Found: C, 71.8; H, 5.6; N, 20.4.

Synthesis of N-(2-pyridyl)aminodiphenylacetic acids 2 and related compounds 6-8. General Procedure. Compound **1** (1.0 g) was disolved in the appropriate nucleophilic solvent by heating. When compound **1** was insoluble an inert co-solvent was added. The resulting solution was refluxed for the time indicated in each case (see Table 4) unless otherwise stated. When the acid derivative did not crystallize by cooling the reaction mixture, the solvent was

Table 2

^{1}H-NMR spectral data for compounds 1

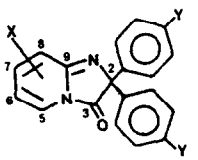


Comp.	X	H-5	H-6	H-7	H-8	Me	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1a	H	7.22	5.92	6.89	6.71	---	6.6	1.15	6.6	---	9.7
1a-HCl	H	7.80	6.54	7.45	6.87	---	5.2	1.8	7.0	0.9	8.5
1b	5-Me	---	5.53	6.72	6.55	2.45	---	---	6.35		9.65
1c	6-Me	7.04	---	6.76	6.67	1.90	---	1.35	---	---	9.75
1d	7-Me	7.24	5.77	---	6.47	2.05	7.3	---	---		---
1e	8-Me	7.25	5.84	6.65	---	2.18	6.35		6.35	---	---

a) Recorded at 300 MHz in $DCCl_3$ except **1a-HCl** (DMSO-d_6), using TMS as internal reference.
b) Aromatic proton resonances appeared between 7.04-7.52 ppm as complex multiplets.

Table 3

^{13}C-NMR spectral data for compounds 1

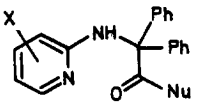


Comp	X	Y	C-2	C-3	C-5	C-6	C-7	C-8	C-9
1a	H	H	78.2	180.0	124.7	108.2	136.6	120.0	155.5
1a-HCl	H	H	70.9	171.5	126.9	113.9	138.7	113.1	152.3
1b	5-Me	H	77.5	181.9	127.2	108.1	136.4	117.6	157.3
1c	6-Me	H	78.0	180.5	121.9	129.0	132.7	108.2	156.2
1d	7-Me	H	77.9	179.4	123.2	111.2	147.7	116.3	155.3
1e	8-Me	H	78.0	180.5	122.0	108.0	135.0	132.6	156.3
1f	6-Cl	H	78.7	178.4	121.8	116.2	138.1	120.5	153.3
1g	8-OMe	H	78.6	179.8	107.7	116.5	107.4	148.8	151.9
1h	8-OH	H	68.5	164.8	122.6	115.3	135.5	146.9	143.7
1i	H	NO_2	76.5	178.1	124.5	109.1	137.8	119.5	156.7
1j	H	OMe	76.7	179.8	124.1	107.6	136.1	119.3	154.7

a) In $DCCl_3$ except **1h** (DMSO-d_6); b) Aromatic carbon resonances appeared between 131.3-145.4 (C-*ipso*), 126.8-127.8 (C-*ortho*), 113.3-128.6 (C-*meta*) and 127.1-158.6 (C-*para*).
c) Assignments might be interchangeable.

Table 4

Synthesis of *N*-(2-Pyridyl)aminodiphenylacetic acids 2 and their derivatives 6-8



Comp	X	Nu	Solvent (ml)	t (h)	Yield (%)	Mp (°C) (solvent)	IR (cm^{-1}) C=O	^{13}C-NMR C=O	^{13}C-NMR CPh_2
2a	H	OH	THF/H_2O (5/2)	3	51	168-170	1665 1625	173.0	70.0
2b	4-Me	OH	THF/H_2O (5/1)	3	90	188-190	1695 1640		
6a	H	OMe	MeOH (5)	0.5	100	130-132 (MeOH)	1720	172.7	70.2
6b	4-Me	OMe	MeOH (15)	6	70	136-138 (MeOH)	1720		
6c	5-Me	OMe	MeOH (15)	6	85	110-112 (MeOH)	1730		
6d	6-Me	OMe	MeOH (10)	3	90	90-92 (MeOH)	1730 1720		
6e	5-Cl	OMe	MeOH (5)	3	75	132-134 (MeOH)	1730		
6f	H	OCH_2Ph	$PhCH_2OH$	18	90	110-111 (EtOAc/hexane)	1750	171.9	70.1
7a	H	HNallyl	THF/allylNH_2 (15/1)	6.5	75	168 (EtOAc)	1670	171.4	69.3
7b	H	$HNCH_2Ph$	Toluene/ $PhCH_2NH_2$ (10/5)	24	100	180 (EtOAc)	1670	171.6	69.2
7c	H	NHi-Pr	i-PrNH_2 (10)	40	65	196-197 (Benzene)	1670	171.6	69.2
7d	H	$HNCH_2CH_2OH$	Ethanolamine/ THF	7	90	132-134 (Toluene)	1655	171.5	69.5
8a	H	$NHNH_2$	THF (15)	0.75	90	133-136 (Toluene)	1660	171.3	68.6
8b	4-Me	$NHNH_2$	THF (15)	3	95	150-152 (Benzene)	1670		
8c	5-Me	$NHNH_2$	THF (14)	12	85	130-132 (Benzene)	1675		
8d	6-Me	$NHNH_2$	THF (15)	0.75	90	160-162 (EtOAc)	1660		

a) Per gram of compound 1. b) At reflux except for 6f (room temperature). c) In pure isolated product with correct analyses. d)In KBr pellet. e) In DMSO-d_6 except for 6f and 7d recorded in $DCCl_3$. f) Equimolar amounts of the reactans were used. g) Along with compound 5a, an additional 30 % of the amine 11a was obtained.

removed *in vacuo* and the resulting crude material was crystallized from the appropriate solvent.

Synthesis of amines 11. These compounds were prepared according to the General Method employed for compounds 6-8, with some minor modifications.

N-(2-Pyridyl)benzhydrylamine (11a). This compound was prepared from 1a (1g). THF (5 ml) and water (2 ml). Reaction time, 22 h. Colorless needles from hexane (60 %), mp 102 °C. IR (KBr) υ 3270 cm^{-1}. ^{1}H-NMR ($DCCl_3$, 80 MHz) δ 5.3 (d, 1H, J= 8.8 Hz, NH), 5.8 (d, 1H, J= 8.8 Hz, CH), 6.1-8.2 (m, 14 H, aromatics). ^{13}C-NMR ($DCCl_3$) δ 60.5 (CPh_2). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.1; H, 6.1; N, 10.8. Found: C, 83.4; H, 6.1; N, 10.6.

N-(4-Methyl-2-pyridyl)benzhydrylamine (11b). This compound was prepared from 1d (1g), THF (10 ml), and water (2 ml). Reaction time, 24 h. Colorless needles from benzene (75 %), mp 110-112 °C. IR (KBr) υ 3240 cm^{-1}. ^{1}H-NMR ($DCCl_3$, 60 MHz) δ 2.1 (s, 3 H, Me), 5.2 (broad, s, 1 H, NH), 5.8 (d, 1H, J= 6.0 Hz, CH), 6.1 (broad, s, 1H, H-3 pyridine), 6.2-6.5 (m, 1H, H-5 pyridine), 7.2 (s, 10 H, aromatics), 7.8 (d, H-6 pyridine). ^{13}C-NMR ($DCCl_3$) δ 60.5 (CPh_2). Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.2; H, 6.6; N, 10.2. Found: C, 83.5; H, 6.6; N, 10.2.

Reaction of 1a with $NaBH_4$/2-propanol. Sodium borohydride (0.17 g, 4.59 mmol) was added in one portion to a boiling solution of 1a (1.0 g, 3.49 mmol) in 2-propanol (60 ml). The resulting reaction mixture was refluxed for 30 min. The former yellow color faded during this time, and the colorless solution was cooled and concentrated to 1/10 of the original volume *in vacuo*. The white solid was collected by suction filtration to obtain 0.52 g (51 %) of compound 12. The mother liquor from 12 were poured onto ice and extracted (ethyl acetate). During the extraction a slight gas formation was observed. After drying ($MgSO_4$) and removing the solvent *in vacuo*, the resulting white solid was chromatographed on silica gel (benzene-ethyl acetate 10:1). Amine 11a (90 mg, 10 %) and aminoalcohol 12 (0.19 g, 19 %) were obtained in elution order. Aminoacid 2a (as its sodium salt) (0.23 g, 20 %) was recovered after elution with methanol. The overall yield in reduction products was nearly quantitative.

2-N-(2-Pyridylamino)2,2-diphenylethanol (12). Colorless needles from ethanol (70 %), mp 220 °C. IR (KBr) υ 3260 (NH, OH) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 4.2 (s, 2H, CH_2), 6.4-6.9 (broad, 2H, NH, OH), 7.0-7.9 (m, 3 H), 7.1-7.4 (m, 11 H). ^{13}C-NMR ($DCCl_3$) δ 157.3, 145.5, 143.6, 137.1, 127.8, 127.5, 126.6, 112.3, 111.0, 69.1 (CH_2OH), 67.8 (Ph_2C). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.6; H, 6.2; N, 9.6. Found: C, 78.4; H, 5.9; N, 9.3.

Sodium 2,2-diphenyl-N-(2-pyridyl)aminoacetate. Colorless powder (20 %). This compound decomposed without melting. IR (KBr) υ 3580, 3340 3040, 1610. ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 5.8 (d, 1H), 6.2 (t, 1H), 6.7-7.9 (m, 12 H). ^{13}C-NMR (DMSO-d_6) δ 173.4 (COO^-), 157.1, 147.8, 142.3, 135.9, 129.0, 126.9, 125.8, 111.3, 107.5, 70.2 (Ph_2C). Anal. Calcd for $C_{18}H_{15}N_2O_2Na$: C, 69.2; H, 4.6; N, 8.6. Found: C, 69.6; H, 4.1; N, 8.6.

Reaction of 1a with $LiAlH_4$ in ether. A freshly prepared saturated solution of $LiAlH_4$ in ether (15 ml) was added dropwise *via* syringe to a solution of 1a (1.0 g) in dry ether. All operations were carried out under dry argon. During the addition, a pale yellow solid appeared. The reaction mixture was stirred at room temperature for 50 min and then cooled to 0 °C. Commercial ether and water were added carefully after this time. After a few minutes, inorganic material was filtered and washed carefully with ether. The collected organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give 0.86 g of a mixture of three compounds (tlc). ^{1}H-NMR analysis of the crude material showed that the main product in the mixture was 5,8-dihydro-2,2-diphenyl-3*H*-imidazo[1,2-a]pyridine, 15. Flash chromatography (silica-gel, benzene/ethyl acetate 1:1) yielded, in elution order, 0.1 g (10 %) of 2-[*N*-(2-pyridylamino]-2,2-diphenylethanol, 12, 0.28 g (30 %) of an equimolar mixture of compounds 15 and 16 and, finally, 0.36 g (38 %) of pure 16.

2,3,5,8-Tetrahydro-2,2-diphenylimidazo[1,2-a]pyridine (15). Pale yellow oil. IR ($HCCl_3$) υ 1610 (C=N) cm^{-1}. ^{1}H-NMR ($DCCl_3$, 300 MHz) δ 3.1 (m, 2H, H-8), 3.6 (m, 2 H, H-5), 3.91 (s, 2 H, H-3), 5.65 (s, 2H, H-6, H-7), 7.0-7.5 (m, 10 H, aromatics). ^{13}C-NMR ($DCCl_3$) δ 158.7 (C=N, C-8a), 147.7 (C-*ipso*), 127.8, 127.6, 126.3, 121.5 and 121.2 (C-6, C-7), 74.8 (C-2), 63.8 (C-3), 46.7 (C-5), 25.4 (C-8).

2,3,5,6-Tetrahydro-2,2-diphenylimidazo[1,2-a]pyridine (**16**). Pale yellow oil. IR ($HCCl_3$) υ 1650 (C=N) cm^{-1}. ^{1}H-NMR ($DCCl_3$, 300 MHz) δ 2.43-2.50 (m, 2 H, H-6), 3.65 (t, 2H, H-5), 3.85 (s, 2 H, H-3). 6.29-6.44 [AB part of an ABX_2 system: 6.32 (d, J = 10.0 Hz, 1H, H-8) and 6.40 (dt, J = 10.0 and 3.9 Hz, 1H, H-7)], 7.1-7.5 (m, 10 H, aromatics). ^{13}C-NMR ($DCCl_3$) δ 159.7 (C=N C-8a), 146.8 (C-7), 137.4 (C-8), 127.8, 127.7, 126.1, 119.6 (C-7), 75.7 (C-2), 63.6 (C-3), 44.9 (C-5), 24.6 (C-6). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 83.2; H, 6.6; N, 10.2. Found: C, 83.2; H, 6.6; N, 10.4.

Synthesis of 2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridin-3-ones, 10. General Procedure. A solution of compound 1 (1.7 mmol) in ethyl acetate (60 ml) was hydrogenated in the presence of Pd-C (10 %, 30 mg) in a Parr-type apparatus at room temperature and an initial pressure of 35 psi (2.45 atm). When no more hydrogen was absorbed, the catalyst was filtered off and the solvent removed under reduced pressure. The white solid crude material was taken up in ether and filtered. Finally, the product was crystallized from the appropriate solvent.

2,2-Diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridin-3-one (**10a**). Reaction time, 3.5 h. Colorless crystals from ethyl acetate (80 %), mp 185-186 °C. IR (KBr) υ 1730 (C=O), 1635 (C=N) cm^{-1}. ^{1}H-NMR ($DCCl_3$, 60 MHz) δ 1.6-2.0 (m, 4 H, H-6, H-7), 2.5-3.0 (m, 2H, H-8), 3.2-3.6 (m, 2H, H-5), 7.0-7.6 (m, 10 H, aromatics). ^{13}C-NMR ($DCCl_3$) δ 181.7 (C=O), 159.8 (C=N), 76.9 (C-2), 40.0 (C-5), 26.5 (C-8), 21.4 (C-7), 19.5 (C-6). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.6; H, 6.2; N, 9.6. Found: C, 78.3; H, 6.0; N, 9.6.

2,2-Diphenyl-8-methyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridin-3-one (**10b**). Reaction time, 2.5 h. Colorless crystals from ethanol (70 %), mp 132-133 °C. IR (KBr) υ 1720 (C=O), 1630 (C=N). ^{1}H-NMR ($DCCl_3$, 60 MHz) δ 1.4 (d, 3H, J= 7.0 Hz, Me), 1.5-2.1 (m, 4H, H-6, H-7), 2.3-2.9 (m, 1H, H-8), 3.1-3.7 (m, 2H, H-5), 6.8-7.5 (m, 10 H, aromatics). ^{13}C-NMR ($DCCl_3$) δ 182.0 (C=O), 163.6 (C=N), 76.9 (C-2), 40.1 (C-5), 31.9 (C-8), 28.1 (C-7), 20.3 (C-6). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.9; H, 6.6; N, 9.2. Found: C, 79.2; H, 6.3; N, 9.5.

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References and notes

1. See, for example: (a) Alcaide, B.; Escobar, G.; Pérez-Ossorio, R.; Plumet, J.; Sanz, D. *J. Chem. Research* (S) 1984, 144; (M) 1984, 1466. (b) Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Rodríguez-Campos, I. M. *Tetrahedron Lett.* 1986, *27*, 1381.

2. See, for example: (a) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J.; Sánchez, M. M. *Tetrahedron Lett.* 1985, *26*, 4403. (b) Alcaide, B.; Dominguez, G.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles*, 1986, *24*, 1579. (c) Alcaide, B.; Dominguez, G.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* 1986, 99. (d) Alcaide, B.; Dominguez, G.; Plumet, J.; Sierra M. A. *Heterocycles* 1988, *27*, 1317. (e) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J.; Rodríguez-López, J. *Tetrahedron Lett.* 1986, *27*, 5129. (f) Alcaide, B.; Gómez, A.; Plumet, J.; Rodríguez-López, J. *Tetrahedron*, 1989, *45*, 2751.

3. (a) Inoue, S.; Sugiura, S.; Kakoi, H.; Goto, T. *Tetrahedron Lett.* **1969**, 1609. (b) Sugiura, S.; Kakoi, H.; Inoue, S.; Goto, T. *Yakugaku Zasshi* **1970**, *90*, 441. (c) Sugiura, S.; Inoue, S.; Goto, T.; *Yakugaku Zasshi*, **1970**, *90*, 707. (d) Barlin, G. B.; Brown, D. J.; Kadunc, Z.; Petric, A.; Stanovnik, B.; Tisler, M. *Aust. J. Chem.* **1983**, 36, 1215. (e) Barlin, G. B.; Brown, I. L.; Galic, L.; Kancic, V. *Aust. J. Chem.* **1982**, 35, 423.

4. (a) Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Sierra, M. A. *Tetrahedron Lett.* **1986**, *27*, 1627. (b) Alcaide, B.; Plumet, J.; Sierra, M. A.; Vicent, C. *J. Org. Chem.* accepted for publication.

5. (a) Sokov, P. G. *J. Gen. Chem.* **1940**, *10*, 1457. (b) Mosby, W.L. "Chem. Heterocyclic Comp., Heterocyclic System with Bridgehead Nitrogen Atoms", ed. by A. Weissberger, Interscience, New York, 1961, *1*(V), pp. 498.

6. Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Sierra, M. A.; Garcia-Blanco, S.; Martínez-Carrera, S. *Tetrahedron Lett.* **1985**, 26, 247.

7. Knott, E. B. *J. Chem. Soc.* **1956**, 1360.

8. Katritzky, A. R.; Caster, K. C.; Rubio, O.; Schwarz, O. *J. Heterocyclic Chem.* **1986**, 23, 1315.

9. Blewitt, H. L. "Special Topics in Heterocyclic Chemistry", ed. A. Weissberger and E. C. Taylor, John Willey, New York, 1977, pp 126.

10. (a) Rydzkowski, R.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett.* **1985**, 26, 2571. (b) Rydzkowski, R.; Blondeau, D.; Sliwa, H.; Cazé, C. *J. Chem. Research* (S), **1986**, 50; (M) **1986**, 670.

11. (a) Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; de la Torre, C. *An. Quím.* **1983**, 79C, 235. (b) Alcaide, B.; Escobar, G.; Pérez-Ossorio, R.; Plumet, J.; Rodríguez-Campos, I. *An. Quím.*, **1985**, 81C, 190.

12. Poje, M.; Perina, I.; Vickovic, I.; Bruro, M. *Tetrahedron* **1985**, *41*, 1985 and earlier references cited therein.

13. Compound **12** was identified by comparison with an authentic sample prepared independently by reduction of methyl *N*-(2-pyridyl)aminodiphenylacetate (**6a**) with $LiAlH_4$ in THF.

14. Independent reaction of **1a** with an aqueous solution of NaOH was instantaneous giving the sodium salt of acid **2a** quantitatively.

15. Due to remarkable sensitivity of compound 1a to bases, a freshly prepared saturated solution of $LiAlH_4$ in ether, under rigorously anhydrous conditions, was used. The use of a suspension of commercial $LiAlH_4$ in ether affords erratic results depending upon the origin of the hydride, with variable amounts of hydroxides.

16. For other examples of differential reactivity of both metal hydrides see, for example: (a) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *An. Quím.* 1982, 78C, 278. (b) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans* 2 1983, 1648.

17. Smith, P. A. S." Open Chain Nitrogen Compounds", Benjamin, New York, 1965, 1 (4), pp 137.

18. Bernstein, J.; Stearns, B.; Dexter, M.; Sott, W. A. *J. Am. Chem. Soc.* 1947, 69, 1147.

19. (a) Chattaway, F. D.; Coulson, E. A. *J. Chem. Soc.* 1928, 1361. (b) Ogata, Y.; Yamashita, M. *Tetrahedron*, 1971, 27, 2725.

20. Hartman, W. W.; Roll, L. J. " Organic Syntheses", ed. by L. I. Smith, John Wiley & Sons, New York, 1943, 23, pp. 1.