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Formation of heterocyclic rings containing nitrogen: Part XXVI—Condensation of pyridine 2, 3-diamine with aromatic aldehydes

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ABSTRACT

Preparation of 3-arylideneamino-2-aminopyridines (I), 2-aryl-1H-2, 3-dihydroimidazo (4, 5-*b*) pyridines (III) and 2-aryl-1H-imidazo (4, 5-*b*) pyridines (IV), by the condensation of pyridine-2, 3-diamine with aromatic aldehydes under different conditions is described.

WHILE the reaction of *o*-phenylenediamine with aromatic aldehydes has been extensively studied, comparatively little work has been done on the condensation of the latter with heterocyclic *o*-diamines. The simplest aza-heterocyclic analogues of *o*-phenylenediamine being diamino-pyridines, the condensation of pyridine–2, 3-diamine with aromatic aldehydes, under different conditions, has been undertaken with a view to study the effect of the pyridine nitrogen on the diamine-aldehyde reactions and the results are presented in this paper. The diamine itself has been prepared from 2-aminopyridine using the procedure of Fox and Threlfall.[1]

REACTION IN METHANOL AT ROOM TEMPERATURE : The diamine, when treated with an equimolar quantity of *p*-methoxybenzaldehyde in methanol at room temperature for 4 hr, yielded a bright yellow crystalline compound (m.p. 136°). Its mass spectrum showed the molecular ion peak at 227 indicating the compound to be 1 : 1 product. The i.r. ($CHCl_3$) spectrum indicated a doublet at 3510 and 3400 cm^{-1} assignable to the $-NH_2$ group. The n.m.r. ($CDCl_3$) spectrum revealed signals at 3·91 δ (s, 3H, $-OCH_3$), 5·08 δ (broad s, 2H, D_2O exchangeable, $-NH_2$), 6·53–8·16 δ (m, 7H, four phenyl and three pyridine protons), 8·58 δ (s, 1H). The signal at 8·58 δ has been assigned to the azomethine proton (–N=CH–) of a Schiff base structure, analogous to benzylideneaniline.[2] All this evidence is compatible with

either of the structures I and II (Ar = *p*-methoxyphenyl, Chart I) for this compound.

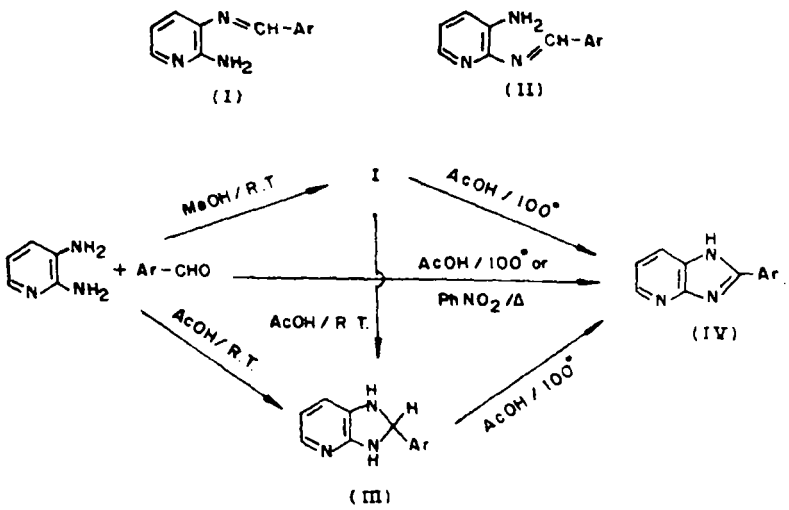

Chart 1. Reactions of pyridine-2, 3-diamine with aromatic aldehydes.

Structure II (Ar = *p*-methoxyphenyl) is less probable since the amino group at 2-position of pyridine ring is less basic than the one at 3-position[3] and the formation of Schiff bases from 2-aminopyridine with aromatic aldehydes is known to occur only under refluxing conditions.[4] Under the conditions of the present reaction, the amino group at 3-position, which behaves like the one in aniline,[4] may preferentially react to give 3-arylidene-amino-2-aminopyridine (I, Ar = *p*-methoxyphenyl). This is further supported by the fact that the 1 : 1 product (I, Ar = *p*-methoxyphenyl) alone is obtained from the reaction in which two moles or more of the aldehyde have been made use of.

REACTION IN ACETIC ACID AT ROOM TEMPERATURE : Reaction of the diamine with *p*-methoxybenzaldehyde, in acetic acid medium, in 1 : 1 molar proportion at room temperature for 2 hr, yielded a pale yellow crystalline compound (m.p. 90°), different from I (Ar = *p*-methoxyphenyl). The former, on treatment with dil. hydrochloric acid at room temperature, gave *p*-methoxybenzaldehyde as one of the products. Its mass spectrum showed the molecular ion peak at 227 indicating it to be isomeric with I (Ar = *p*-methoxyphenyl). The i.r. (KBr) spectrum showed a single absorption at 3450 cm^{-1} assignable to the –NH– stretching. On this basis, 2-(*p*-methoxyphenyl)-1H-2, 3-dihydroimidazo (4, 5-*b*) pyridine (III, Ar = *p*-methoxyphenyl) structure has been assigned for this compound.

III (Ar = *p*-methoxyphenyl) appears to breakdown in organic solvents like $CHCl_3$ or CCl_4, since its i.r. spectrum in these solvents revealed a peak at 1705 cm^{-1} in the carbonyl region. It may be mentioned here that Garner *et al*[5] reported a similar breakdown of 2, 3-dihydrobenzimidazole-2-spirocyclohexane in organic solvents like $CHCl_3$ or CCl_4.

The reaction in methanol and in acetic acid has been extended to seven other aldehydes, and the products obtained have been assigned, by analogy and on the basis of i.r. spectra, structures I and III respectively (table 1).

3-Arylideneamino-2-aminopyridines (I) may reasonably be expected to be the intermediates in the reaction in acetic acid medium, the latter facilitating their isomerisation to the respective 2-aryl-1H-2, 3-dihydro-imidazo (4, 5-*b*)-pyridines (III). This has been confirmed independently in each case by the conversion of I to III by treatment with acetic acid at room temperature. This isomerisation appears to take place by protonation of the azomethine nitrogen followed by nucleophilic attack by the nitrogen of the 2-amino group on the positively charged carbon-atom of the arylidene moiety.

The 3-arylideneamino-2-aminopyridine (I) and the dihydroimidazo-pyridine (III, Ar = *p*-methoxyphenyl) showed common fragmentation

Table 1. Products of condensation of pyridine-2, 3-diamine with aromatic aldehydes

Sl. No.	Ar–CHO used Ar =	3-Arylideneamino-2-aminopyridine (I)		Dihydroimidazo-pyridine (III)		Imidazo-pyridine (IV)	
		m.p. °C	% yield	m.p. °C	% yield	m.p. °C	% yield
1.	Phenyl	128[a]	45	67	40	289[c] (lit. 293)[10]	35
2.	*p*-Methylphenyl	134[a]	55	80	35	260[c] (lit. 261)[10]	30
3.	*p*-Hydroxyphenyl	207[b]	88	119	60	above 340[d]	55
4.	*p*-Methoxyphenyl	136[a]	80	90	30	238[c]	30
5.	*p*-Chlorophenyl	143[a]	75	93	50	339[c] (lit. 333)[10]	50
6.	*p*-Nitrophenyl	214[c]	95	..	70	above 340[d]	65
7.	*m*-Nitrophenyl	151[c]	80	121	67	above 340[d]	60
8.	*o*-Nitrophenyl	140[a]	50	74	40	249[c]	28

The recrystallisation solvents used were (*a*) Pet. ether-Benzene, (*b*) Benzene, (*c*) Benzene Methanol and, (*d*) Methanol.

Numbers in superscript relate to reference.

pattern in their mass spectra, only the relative intensities being different (Chart II).

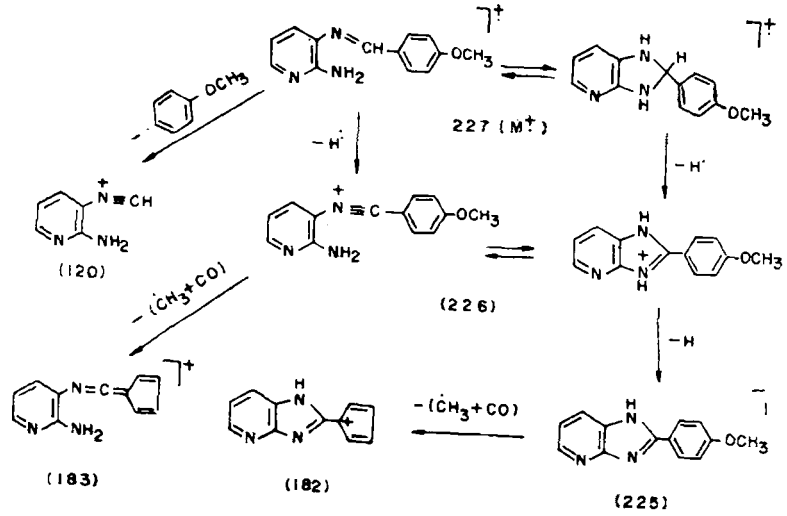

Chart 2. Mass spectral fragmentation of I and III (Ar = *p*-methoxyphenyl).

REACTION IN ACETIC ACID AT 100° : The diamine on heating with *p*-methoxybenzaldehyde, in acetic acid medium, on a steam-bath for 4 hr gave a product (m.p. 238°). This product dissolved readily in dil. hydrochloric acid and could be reprecipitated unchanged on neutralisation. Its molecular ion peak was found to be at 225, two units less than I and III (Ar = *p*-methoxyphenyl). In the i.r. (KBr) spectrum, it showed a broad band around 3110 cm^{-1}, assignable to –NH– stretching. The broad nature of this absorption is similar to the one due to the –NH– grouping of 2-phenylbenzimidazole.[6] The n.m.r. (TFA) spectrum revealed signals at 3·58 δ (s, 3H, $-OCH_3$), 6·58 and 7·79 δ (4H, AB-system, *p*-disubstituted phenyl protons), 7·51 δ (m, 1H, C_6–H), 8·38 δ (m, 2H, C_5–H and C_7–H). Since the spectrum was recorded in TFA, –NH– could not be located. This compound could also be obtained by refluxing the diamine and *p*-methoxybenzaldehyde in nitrobenzene medium,[7] in 1 : 1 molar proportion. On the basis of this evidence, the compound has been assigned 2-(*p*-methoxyphenyl)-1H-imidazo (4, 5-*b*) pyridine structure (IV, Ar = *p*-methoxyphenyl).

Obviously, dehydrogenative cyclisation assisted by air, is taking place in the reaction carried out in hot acetic acid. This reaction has been extended to seven other aldehydes and the products obtained have been assigned imidazopyridine structures (IV), by analogy and by i.r. spectra which showed a broad –NH– stretching around 3100 cm^{-1} in each case.

That a 3-arylideneamino-2-aminopyridine (I) and the corresponding dihydroimidazopyridine (III) are intermediates in this reaction has been shown by converting I and, independently III, into IV (Ar = *p*-methoxyphenyl) by heating with acetic acid for four hours on a steam-bath.

In the reaction of *o*-phenylenediamine with aromatic aldehydes in methanol medium, mono-anils and, in certain cases, di-anils are known to be formed[8] depending upon the nature of the aldehyde and the molar proportions used in the reaction. In acetic acid medium, at room temperature, cyclic products such as 2-arylbenzimidazole (a 1 : 1 product) and 1-arylmethyl-2-arylbenzimidazole (a 1 : 2 product) are obtained.[8] However, pyridine-2, 3-diamine in methanol medium yielded, without exception, 3-arylideneamino-2-aminopyridines irrespective of the molar proportions used in the reaction. These mono-anils could be smoothly isomerised to the dihydroimidazopyridines by treatment with acetic acid at room temperature. The independent isolation of mono-anils (I) and dihydroimidazopyridines (III), and the isomerisation of I to III appears to be the first instance in a 1, 2-diamine-aldehyde reaction. In the case of *o*-phenylenediamine, the benzimidazolines could not be isolated in a free-state and they were shown to be in tautomeric equilibrium with the corresponding mono-anils by n.m.r. spectroscopy.[9]

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Perkin-Elmer infracord 337 n.m.r. spectra on Varian A60–D and mass spectra on Perkin-Elmer Hitachi RMU–6L instruments.

1. 3-ARYLIDENEAMINO-2-AMINOPYRIDINES (I) : Pyridine-2, 3-diamine (0·55 g) was dissolved in minimum amount of methanol at room temperature and an equimolar quantity of the aldehyde was added. The reaction mixture was stirred well and set aside at room temperature for four hours or more with occasional stirring and scratching until solid separates. The solid, that separated was filtered, washed with a few drops of methanol followed by petroleum ether (60–80°, 5 ml) and dried. The crude 3-arylideneamino-2-aminopyridines thus obtained were recrystallised from suitable solvents (table 1).

2. 2-ARYL-1H-2, 3-DIHYDROIMIDAZO (4, 5-*b*) PYRIDINES (III) : Pyridine-2, 3-diamine (0·55 g) was dissolved in minimum amount of acetic acid and an equimolar quantity of the aldehyde was added. The resulting solution was well stirred and set aside at room temperature. In the case of *p*-hydroxy, *p*-nitro and *m*-nitrobenzaldehydes, crystalline solids separated from the

clear solution after 2 hr or more whereas in the case of benzaldehyde, *p*-methyl, *p*-methoxy, *p*-chloro and *o*-nitrobenzaldehydes, a syrupy liquid was obtained which on repeated trituration with petroleum ether yielded solid products. III, thus obtained, were filtered, washed with petroleum ether and dried (table 1).

3. 2-ARYL-1H-IMIDAZO (4, 5-*b*) PYRIDINES (IV) :

(i) IN ACETIC ACID : A solution of pyridine-2, 3-diamine (0·55 g) and an equimolar quantity of the aldehyde in acetic acid (10 ml) was heated on a steam-bath for 4 hr. The reaction mixture was then cooled to room temperature and diluted with water (30 ml) when a resinous material separated which was triturated with petroleum ether. The fine solid thus obtained was recrystallised from a suitable solvent (table 1).

(ii) IN NITROBENZENE : The diamine (0·55 g) was suspended in 10 ml of nitrobenzene and an equimolar quantity of *p*-methoxybenzaldehyde was added. The mixture was then refluxed for 1½ hr and steam-distilled. The residue was filtered and recrystallised from benzene-methanol mixture to the pure product, m.p. and m.m.p. with the one obtained in the reaction 3 (i) above using the same aldehyde, 238°.

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