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SYNTHESES FROM PYRIDINE ALDEHYDES—III

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Abstract—The synthesis of 5[*H*]-pyrindines has been carried out starting with an azlactone derived from 6-methylpyridine-2-aldehyde. The significance of this in relation to previous unsuccessful attempts to make similar compounds starting from pyridine-2-aldehyde is discussed.

IT HAS been reported recently[1] that unsaturated azlactones obtained from pyridine 4- and 3-aldehydes and hippuric or aceturic acid react with Grignard reagents to yield 6[*H*]- or 7[*H*]-pyrindines. In some instances this proceeds by way of intermediate carbinols or oxazolines but, on occasions, it occurs directly.

An attempt to synthesize 5[*H*]-pyrindines by a similar route[2] proved unsuccessful since although the unsaturated azlactone derived from pyridine-2-aldehyde reacted with Grignard reagents to give (usually) a carbinol the latter did not undergo the further cyclization stage.

The apparent anomaly between an intramolecular carbonium ion attack taking place at position 3 of the pyridine ring when the side chain was attached at position 4 but not when attached at position 2 was not explained.

However, the possibility that this is due to a relatively greater contribution from the inductive effect of the N atom rather than from mesomeric interactions could be investigated by studying the analogous reactions of the unsaturated azlactone of 6-methylpyridine-2-aldehyde in which the nitrogen inductive effect would be partly offset by the electron-donating effect of the Me substituent. Moreover, this approach is also suggested by the recent independent observation[3] which proposes that a 5[*H*]-pyridine, viz. 2,5-dimethyl-6-phenyl-5(4*H*)]-pyridine may have been obtained by condensation of 6-methylpyridine-2-aldehyde with phenylacetone and reduction of the 3-phenyl-4-[6-methyl-2-pyridyl-]3-but-2-one with Zn/HBr.

In order to investigate this problem the preparation of the azlactone derived from 6-methylpyridine-2-aldehyde and hippuric acid has been attempted by several methods previously described[1,2] always resulting in tarry products from which the pure azlactone was separated by column chromatography in low yield. This compound was reacted with phenylmagnesium, bromide, *p*-chlorophenylmagnesium bromide and *p*-anisylmagnesium bromide and the results are summarized in Table 1.

In examples (i) and (ii) tertiary carbinols of structure I were obtained, identified spectroscopically and by comparison with similar compounds previously prepared; while in example (iii) the oxazoline II was formed and similarly identified.

Treatment of the carbinols from (i) and (ii) by heating with a mixture of glacial acetic–HCl at 40° resulted in the formation of oxazolines corresponding to the product of reaction (iii).

TABLE 1. a REACTION OF 2-PHENYL-2-6-METHYLPICOLYLIDENE-5(4*H*)-OXAZOLONE WITH GRIGNARD REAGENTS AND b SUBSEQUENT CONVERSION TO 5*H*-PYRINDINES

(a)	Grignard substituent	Product obtained	M.p. °C	Yield	Found C	Found H	Found N	Analyses % empirical formula	Requires C	Requires H	Requires N
(i)	C_6H_5-	Carbinol	165	16·8	79·41	5·64	6·26	$C_{28}H_{24}N_2O_2$	80·00	5·72	6·67
(ii)	$C_6H_4Cl(p)-$	Carbinol	157	17·9	68·52	4·69	5·28	$C_{28}H_{22}N_2O_2Cl_2$	68·71	4·51	5·73
(iii)	$C_6H_4OCH_3(p)-$	Oxazoline	172	22·9	77·26	5·42	6·96	$C_{30}H_{26}N_2O_3$	77·93	5·63	6·06

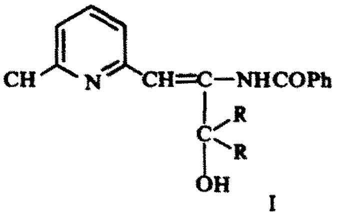
(b)	Grignard substituent	Starting material	M.p. °C	Yield	Found C	Found H	Found N	Analyses empirical formula	Requires C	Requires H	Requires N
(iv)	C_6H_5-	Carbinol (i)	189	82·1	83·76	5·47	6·99	$C_{28}H_{22}N_2O$	83·58	5·63	6·97
(v)	$C_6H_5Cl(p)-$	Carbinol (ii)	199	79·3	71·69	4·21	5·07	$C_{28}H_{20}N_2OCl_2$	71·34	4·25	5·95
(vi)	$C_6H_5OCH_3(p)-$	Oxazoline (iii)	190	69·4	77·77	5·21	5·82	$C_{30}H_{26}N_2O_3$	77·93	5·63	6·06

NOTES:

(i) Compounds (i) and (iii) and (iv) to (vi) were obtained as white crystals; compound (iii) as yellow crystals.

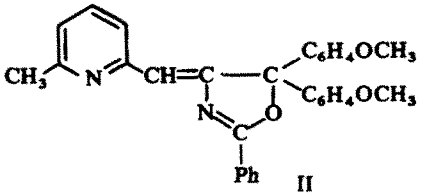
(ii) Compounds (i) and (v) were recrystallized from ethanol, compounds (ii) and (iv) from benzene–pet. ether (40–60°) and compounds (iii) and (vi) from pet. ether (60–80°).

(iii) IR spectral data was obtained for all compounds using the Unicam SP200 (KBr wafer discs). Compounds (i) and (ii) showed characteristic frequencies of —OH(3450 cm^{-1}), —NH(3250 cm^{-1}); amide I (1690 cm^{-1}) and amide II (1620 cm^{-1}); Compound (iii) showed the characteristic frequency of $>$C=N (1650 cm^{-1}); compounds (iv) to (vi) showed the bands characteristic of —NH(3250 cm^{-1}), amide I (1690 cm^{-1}) and amide II (1620 cm^{-1}).



R = C_6H_5– and C_6H_4Cl-

I



II

Further treatment of all three oxazolines in the presence of the same reactants but at an elevated temperature (75°) resulted in a high yield rearrangement to 5-[*H*]-pyrindines, again identified spectroscopically and by comparison with the 6[*H*]- and 7[*H*]-pyrindines previously reported.

Similar rearrangement did not in any case reported[2] result in interconversion of the corresponding compounds of the pyridine-2-aldehyde series to 5[*H*]-pyrindines and thus these results support the suggestion that in these cyclization reactions the inductive interactions are relatively more important than the mesomeric interactions.

EXPERIMENTAL

Preparation of 2-*phenyl*-2-[6-*methylpicolylidene*]5(4H) *oxazolone*-(I). A mixture of hippuric acid (4·5 g) and $KHCO_3$ (1 g) was dissolved in Ac_2O (50 ml) with heating and stirring and then cooled to 0°, 6-methylpyridine-2-aldehyde (3·5 g) was added and the mixture stirred (2 hr). The tarry product was poured into hot water (500 ml) separated by extraction with ether (50 ml × 2) and separated using column chromatography on silica dissolving the crude product in the minimum amount of $CHCl_3$ and eluting with $CHCl_3$–EtOH (9:1).

The product was characterized by its IR spectrum (showing characteristic frequencies of azlactone carbonyl (1785 cm^{-1}), $>C{=}N$ (1650 cm^{-1}), and UV spectrum (high intensity band at λ 362 mμ; less intense band at λ 259 mμ).

General procedure for the reaction of 2-*phenyl*-2-[6-*methylpicolylidene*]-5(4H)*oxazolone with Grignard reagents* (II). To an ethereal soln of Grignard reagent prepared from Mg (0·5 g) and aryl halide (0·025 mole) in ether (30 ml) was added a fine suspension of oxazolone (1·5 g) in ether (30 ml) over one hr. The reaction mixture was refluxed for two hr, left overnight and hydrolysed with sat. NH_4Cl aq. The ether layer was separated, dried over Na_2SO_4 and most of the ether removed. The oily residues obtained were triturated with pet. ether (b.p. 40–60°) and allowed to cool. The products were filtered and recrystallized as indicated in Table 1.

Cyclization of carbinols derived from 2-*phenyl*-2[-6-*methylpicolylidene*]-5(4H) *oxazolone with Grignard reagents* (III). To a fine suspension of carbinol or oxazoline (0·25 g) in AcOH (10 ml) HCl (5 ml, S.G. 1·18) was added slowly. The solid dissolved and the mixture was kept at 75° for 15 min. A white ppt (the pyridine) separated after addition of a sat. soln of NaOAc. This was filtered, washed with water and recrystallized as indicated in Table 1.

REFERENCES

[1] G. Slater and A. W. Somerville, *Tetrahedron* **22**, 35–42 (1966).
[2] G. Slater and A. W. Somerville, *Ibid*. **23**, 2823–2828 (1967).
[3] B. Reichert and A. Lechrer, *Arzreimittel-Forsch*, **15** (1), 36 (1965).