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SYNTHESES FROM PYRIDINE ALDEHYDES—II

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Abstract—The azlactone derived from pyridine-2-aldehyde has been made and its reaction with Grignard reagents studied. The reactivity of the side chain double bond in the three unsaturated azlactones of the pyridine series has been examined and both the saturated and unsaturated azlactones have been converted into the corresponding amino acids.

RECENTLY we reported[1] that carbinols and oxazolines obtained by reaction of the azlactones derived from pyridine 3- and 4-aldehydes with Grignard reagents could be cyclized to 7[H]- and 6[H]-pyrindines.

In the present work similar experiments have been attempted starting with pyridine-2-aldehyde. In this case the azlactone could not be made directly since reaction of pyridine-2-aldehyde with hippuric acid[2] yielded only tarry products. However, on reacting pyridine-2-aldehyde acetal with hippuric acid under the same conditions the free azlactone was obtained in 22% yield together with a small amount of the sulphan adduct.

Tertiary carbinols or oxazolines of the series were obtained as in the earlier work, the product depending on the nature of the substituent group present in the Grignard reagent (Table 1) but in this series attempts at cyclization using a variety of conditions (HCl–glacial AcOH; polyphosphoric acid; BF_3–AcOH complex) proved unsuccessful.

Non-cyclization at position 1 to yield a pyrrocoline is not surprising since this would require carbonium ion attack at a protonated nitrogen atom. Non-cyclization at position 3 is more difficult to explain. In pyridine itself position 3 is the most susceptible to electrophilic attack although the process is not easy while position 2 is highly deactivated, but the analogous cyclization (carbonium ion) reactions in the pyridine 3- and 4-aldehyde series occur readily at positions 3 and 2.[1] Further investigations on this point are in progress.

The reactivity of the side chain double bond of all three azlactones of the pyridine series has also been studied by considering its reactions with a variety of electron-deficient or dipolar species. The reactions studied were those with diazomethane, dimethylsulphoxonium ylide and several 1:3-dipoles (including phenyl azide and butadiene).

Of these only the carbene trapping and ylide addition reactions proved successful.

On reaction with diazomethane cyclopropane derivatives were obtained (Table 2) similar to those obtained from benzaldehyde azlactone[3] and these underwent reaction with Grignard reagents to yield carbinols in the pyridine 2- and 3-aldehyde series and 4:5-cyclopropane 6[H]-pyrindine derivatives in the pyridine-4-aldehyde series.

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[1] G. Slater and A. W. Somerville, *Tetrahedron* **22**, 35 (1966).

[2] E. Baltazzi and E. A. Davis, *Chem. & Ind.* 929 (1962).

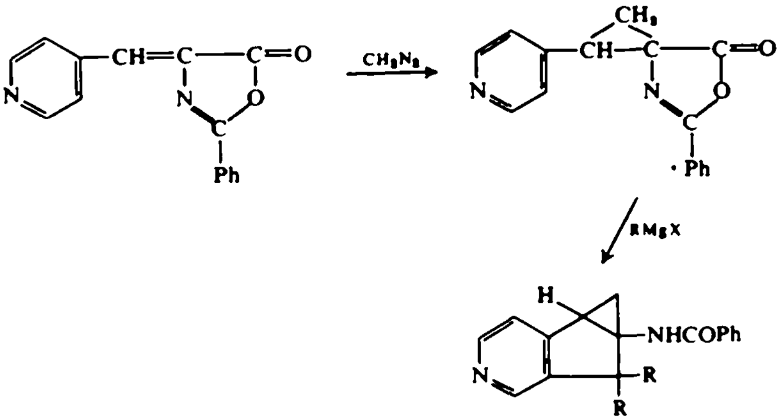
[3] W. I. Awad, R. K. Fateen and M. A. Zayed, *Tetrahedron* **20**, 891 (1964).

TABLE 1. REACTION OF AZLACTONE DERIVED FROM PYRIDINE-2-ALDEHYDE WITH GRIGNARD REAGENTS

Grignard substituent	Product obtained	M.p.	Yield %	Solvent of recrystallization	Colour with conc. sulphuric acid	Found C;	Found H;	Found N;	Found Cl	Analyses % Empirical formula	Requires C;	Requires H;	Requires N;	Requires Cl.
(i) C_6H_5-	Carbinol	142°	54	95% Ethanol	Orange	78·9;	5·31;	6·71;	—	$C_{27}H_{22}O_2N_2$	79·80;	5·42;	6·89;	—
(ii) $C_6H_4Cl(o)$-	Carbinol	156°	36	Benzene	Orange	67·52;	4·11;	5·72;	14·75	$C_{27}H_{20}O_2N_2Cl_2$	68·02;	4·30;	5·90;	14·90
(iii) $C_6H_4Cl(p)$-	Carbinol	172°	61	Benzene/Pet Ether 60–80°	Orange	68·11;	4·24;	5·82;	14·80	$C_{27}H_{20}O_2N_2Cl_2$	68·02;	4·30;	5·90;	14·90
(iv) $C_6H_4OCH_3(o)$-	Carbinol	153°	57	Pet Ether 60–80°	Orange	73·71;	5·72;	6·10;	—	$C_{29}H_{26}O_4N_2$	74·68;	5·58;	6·01;	—
(v) $C_6H_4OCH_3(p)$-	Carbinol	175°	41	Pet Ether 60–80°	Violet	74·20;	5·61;	6·08;	—	$C_{29}H_{26}O_4N_2$	74·68;	5·58;	6·01;	—
(vi) CH_3-	Oxazoline	153°	31	Benzene/Pet Ether 60–80°	Orange	76·80;	5·90;	10·39;	—	$C_{17}H_{16}ON_2$	77·27;	6·06;	10·61;	—

Notes: (1) Compounds (i) to (v) were obtained as white crystals; compound (vi) as pale yellow crystals. (2) IR Spectral data was obtained for all compounds using the Perkin-Elmer Infracord (KBr wafer discs) Compounds (i) to (v) showed characteristic frequencies of —OH (3450–3350 cm^{-1}), —NH (3250–3300 cm^{-1}); amide I (1690–1680 cm^{-1}) and amide II (1620–1590 cm^{-1}). Compound (v) showed the characteristic frequency of >C=N (1655 cm^{-1}).

Thus in the case of the pyridine-4-aldehyde azlactone:



The reactivity pattern of the pyridine azlactones containing the cyclopropane ring is the same as that found in the unsaturated azlactones.

Thus in the pyridine-4-aldehyde series 6[H]-pyrindines were obtained directly (Table 3) while in the pyridine-3-aldehyde series carbinols were obtained (Table 3) which could be cyclized to 5:6-cyclopropane 7[H]-pyrindines (Table 4) and in the pyridine-2-aldehyde series carbinols were obtained (Table 3) which defined cyclization.

The retention of the cyclopropane ring in the structure throughout the various reaction procedures and the structures of the products obtained were shown by reference to their NMR and IR spectra compared with that of known compounds and as detailed in footnotes to the Tables.

The same tricyclic products were obtained by reaction of the unsaturated azlactones with dimethylsulphoxonium ylide, intermediate and unstable sulphur containing compounds being obtained in small amounts as by products the cyclopropane derivatives being obtained in overall higher yields than those obtained using diazomethane (Table 2).

The pyridyl alanines and pyridyl acrylic acids corresponding to the saturated and unsaturated azlactones were made by hydrolysis and compared in physical properties with the same compounds made by earlier workers using other routes.[4–9] In general, however, the m.ps and yields were higher than those initially reported (Tables 5 and 6).

TABLE 2. FORMATION OF CYCLOPROPANE DERIVATIVES FROM UNSATURATED PYRIDINE AZLACTONES

Aldehyde	% yield from diazomethane reaction	% yield from ylide reaction	M.p.	Analyses % Found C; H; N.	Analyses % Empirical formula	Analyses % Requires C; H; N.
4	17	22	152°	72·12; 4·38; 10·64	$C_{16}H_{12}O_2N_2$	72·72; 4·55; 10·61
3	15	25	145°	71·89; 4·35; 10·67	$C_{16}H_{12}O_2N_2$	72·72; 4·55; 10·61
2	12	19	141°	72·31; 4·29; 10·54	$C_{16}H_{12}O_2N_2$	72·72; 4·55; 10·61

NMR spectra are in agreement with a 3-membered ring, revealing an ABX system in the region 2–3·5 ppm.

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TABLE 3. REACTION OF CYCLOPROPANE-PYRIDINE AZLACTONES WITH GRIGNARD REAGENTS

Grignard substituent	Product obtained	M.p. °C	Yield %	Solvent of recrystallization	Found C; H; N; Cl	Analyses % empirical formula	Requires C; H; N; Cl.
(A) 4-Aldehyde							
(i) Ph-	6 [H] pyrindine	202	59	EtOH	81·9; 5·9; 7·1; —	$C_{28}H_{22}ON_2$	83·6; 5·5; 7·0; —
(ii) $C_6H_4Cl(p)$	6 [H] pyrindine	176	41	Benzene/Pet ether	71·1; 4·4; 5·9; 14·9	$C_{28}H_{20}ON_2Cl_2$	71·3; 4·2; 6·0; 15·1
(iii) $C_6H_4OMe(o)$	Carbinol	149	62	Benzene/Pet ether	74·2; 6·0; 5·9; -	$C_{30}H_{28}O_4N_2$	75·0; 5·8; 5·8; —
(B) 3-Aldehyde							
(i) Ph-	Carbinol	141	49	EtOH	78·5; 5·8; 6·6; —	$C_{28}H_{24}O_2N_2$	80·0; 5·7; 6·7; —
(ii) $C_6H_4Cl(p)$	Carbinol	157	46	Benzene	67·7; 4·7; 5·7; 14·7	$C_{28}H_{22}O_2N_2Cl_2$	68·5; 4·5; 5·5; 14·6
(iii) $C_6H_4OMe(o)$	Carbinol	146	74	EtOH	74·1; 5·6; 6·0; --	$C_{30}H_{28}O_4N_2$	75·0; 5·8; 5·8; --
(C) 2-Aldehyde							
(i) Ph-	Carbinol	148	57	EtOH	78·9; 5·7; 6·6; —	$C_{28}H_{24}O_2N_2$	80·0; 5·7; 6·7; —
(ii) $C_6H_4Cl(p)$	Carbinol	165	54	Benzene	67·9; 4·8; 5·7; 14·3	$C_{28}H_{22}O_2N_2Cl_2$	68·5; 4·5; 5·5; 14·6
(iii) $C_6H_4OMe(o)$	Carbinol	142	64	Benzene	73·7; 5·7; 5·9; —	$C_{30}H_{28}O_4N_2$	75·0; 5·8; 5·8; —

IR spectral data was obtained for all compounds using the Perkin-Elmer Infracord (KBr wafer discs). All carbinols showed characteristic frequencies of —OH (3500–3350 cm^{-1}), —NH (3250–3300 cm^{-1}), amide I (1690–1680 m^{-1}) and amide II (1620–1590 cm^{-1}). 6 [H]-pyrindines showed characteristic bands —NH at 3250 cm^{-1} amide I at 1690 cm^{-1}, and amide II at 1620 cm^{-1}.

TABLE 4. CONVERSION OF CARBINOLS TO PYRINDINES

Grignard Substituent	M.p.°C	Yield %	C; H; N; Cl	Analyses % empirical formula	C; H; N; Cl
(A) 4-Aldehyde					
$C_6H_4OMe(o)$	176	68	76·8; 5·6; 6·2; —	$C_{30}H_{26}O_3N_2$	77·9; 5·6; 6·1; —
(B) 3-Aldehyde					
(i) Ph-	207	74	83·2; 5·7; 7·0; —	$C_{28}H_{22}ON_2$	83·6; 5·5; 7·0; —
(ii) $C_6H_4Cl(p)$	175	51	71·0; 4·5; 6·1; 15·1	$C_{28}H_{20}ON_2Cl_2$	71·3; 4·2; 6·0; 15·1
(iii) $C_6H_4OMe(o)$	192	69	76·1; 5·7; 6·3; —	$C_{30}H_{26}O_3N_2$	77·9; 5·6; 6·1; —

IR spectral data was obtained for all compounds using the Perkin-Elmer Infracord (KBr wafer discs). All showed characteristic bands —NH at 3250 cm^{-1}; amide I at 1690 cm^{-1}, and amide II at 1620 cm^{-1}.

TABLE 5. PYRIDYL ALANINES DERIVED FROM PYRIDINE AZLACTONES

	Yield %	Observed M.p.	Literature M.p.	Found % C; H; N.	Analysis % empirical formula	Requires % C; H; N.
4-Pyridyl Alanine	65	265–270°	250–252° (4)	57·67; 5·90; 16·82	$C_8H_{10}N_2O_2$	57·83; 6·0; 16·87
3-Pyridyl Alanine	72	278–280°	262–263° (5)	57·60; 5·57; 16·98	$C_8H_{10}N_2O_2$	57·83; 6·0; 16·87
2-Pyridyl Alanine	62	209–212°	209–210° (6)	57·56; 6·02; 17·14	$C_8H_{10}N_2O_2$	57·83; 6·0; 16·87

IR spectral data was obtained using the Perkin-Elmer Infracord (KBr wafer discs)
Compounds showed the characteristic frequencies:

3060 — 2950, 2540, 2150 cm^{-1} —NH_3^+
1620 cm^{-1} NH_3^+ asym bending
1590 cm^{-1} COO^- asym stretching
1505 cm^{-1} NH_3^+ sym stretching
1410 cm^{-1} COO^- sym
1200 cm^{-1} NH_3^+ rocking
1150 cm^{-1} NH_3^+ rocking
770 cm^{-1} COO^- scissoring

M.p. apparatus was preheated to 200°.

TABLE 6. PYRIDYL ACRYLIC ACIDS DERIVED FROM PYRIDINE AZLACTONES

	Yield %	Observed M.p. °C	Literature M.p. °C	Found % C; H; N.	Analysis % Empirical formula	Requires % C; H; N.
4-Pyridyl Acrylic Acid	80	230°	228° (7)	57·95; 5·41; 16·91	$C_8H_9O_2N_2$	58·18; 5·45; 17·0
3-Pyridyl Acrylic Acid	76	236–241°	235–238° (8)	57·84; 5·30; 16·90	$C_8H_9O_2N_2$	58·18; 5·45; 17·0
2-Pyridyl Acrylic Acid	83	206°	204° (9)	57·92; 5·40; 16·79	$C_8H_9O_2N_2$	58·18; 5·45; 17·0

EXPERIMENTAL

Pyridine-2-aldehyde acetal (I). A mixture of freshly distilled pyridine-2-aldehyde (37·5 g), orthoformic ester (57·0 g), abs EtOH (49·0 g) and powdered NH_4Cl (0·75 g) was refluxed 4 hr, distilled under reduced press (14 mm) and the fraction distilling below 100° set aside prior to refluxing with further NH_4Cl (0·75 g) for 4 hr. The product was combined with the initial residue and further distilled collecting the pale yellow liquid b.p. 109° (12 mm).

Re-distillation under N gave 43·0 g (68%) of a colourless liquid, b.p. 110–112° (14 mm).

2-phenyl-2-picolylidene-5(4H) *oxazolone* (II). Procedure identical to that of Slater and Somerville[1] employed in the pyridine 3- and 4-aldehyde series using the equivalent amount of pyridine-2-aldehyde acetal. The material was recrystallized from benzene, m.p. 162°.

General procedure for the preparation of cyclopropane derivatives of the pyridine azlactones (III)

(a) *Using diazomethane*. The azlactone (2·0 g) was dissolved in dioxan (30 ml) and a soln of diazomethane added generated from nitrosomethlurea (1·2 g) in ether (200 ml).

The reaction mixture was allowed to stand overnight at room temp under anhyd conditions. Removal of the solvent *in vacuo* at room temp left a gummy mass which was suspended in AcOEt to remove the gum. The residue was triturated with pet. ether (40°–60°) and the white crystalline material filtered off.

(b) *Using dimethyl sulphoxium ylide*. The ylide was prepared by the method of Corey and Chaykowsky[10] using NaH (0·05 mole) and DMSO (20 ml), quaternized with MeI and employed directly.

The azlactone (2·0 g) dissolved in DMSO (10 ml) was added to the soln of the ylide and stirred under argon for 48 hr.

The solvent was removed under reduced press leaving a gummy mass which was suspended in AcOEt and the gum removed. The residue was triturated with pet. ether (40–60°) and the white crystalline material filtered off.

In the reaction of oxazolones and cyclopropane derivatives of oxazolones with Grignard reagents—IV the procedure was identical to that employed by Slater and Somerville[1] in the pyridine 3- and 4-aldehyde series.

General procedure for the preparation of pyridyl alanines—V

To a stirred mixture of azlactone (0·1 mole), red P (0·64 g atom) and Ac_2O (67·5 g) was added HI (104 g, 0·38 mole 54%) over 1 hr. The mixture was refluxed for 4 hr, cooled and filtered with suction. The unreacted P was washed on the filter with glacial AcOH and the filtrate and washings were evaporated to dryness under reduced press. Water (100 ml) was added to the residue and again evaporated to dryness. To the residue was added ether (150 ml) and water (150 ml) and the mixture shaken until soln was complete. The aqueous layer was extracted with ether (50 ml × 3) and the ether extracts discarded. The aqueous soln was heated on a steam bath with charcoal (3·0 g) and a trace of Na_2SO_4 added until all dissolved ether was removed after which the soln was filtered, heated to boiling, neutralized with 15% NH_4OH and evaporated to a small bulk (20 ml) when colourless plates separated which were filtered off washed with 95% EtOH and finally with ether. The product was recrystallized from water.

General procedure for the preparation of pyridylacrylic acids—VI

To the azlactone (12·5 g, 0·05 mole) suspended in water (1200 ml) and stirred was added NaOH (2·2 g, 0·055 mole) added as a 10% soln. The mixture was heated on a steam bath for 4 hr, filtered and acidified with HCl when the α-benzoylamino-β-(2-,3- and 4-) pyridylacrylic acids separated and were recrystallized from 95% EtOH.

The benzoylated acids (5·0 g) were refluxed with HCl (1:1, 100 ml) and AcOH was added until soln was obtained after which reflux was continued for 20 hr. The soln was charcoaled and the filtrate evaporated to a small bulk. The benzoic acid was extracted with ether, the aqueous layer was made alkaline with 20% NaOHaq, filtered and acidified with AcOH. The ppt was filtered off and recrystallized from water.

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[10] E. J. Corey and M. Chaykowsky, *J. Am. Chem. Soc.*, 87, 1345 (1965).