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NOVEL RING OPENING OF AMINOHETEROCYCLES: FACILE SYNTHESES OF ω-ALKYLAMINOPENTADIENENITRILES

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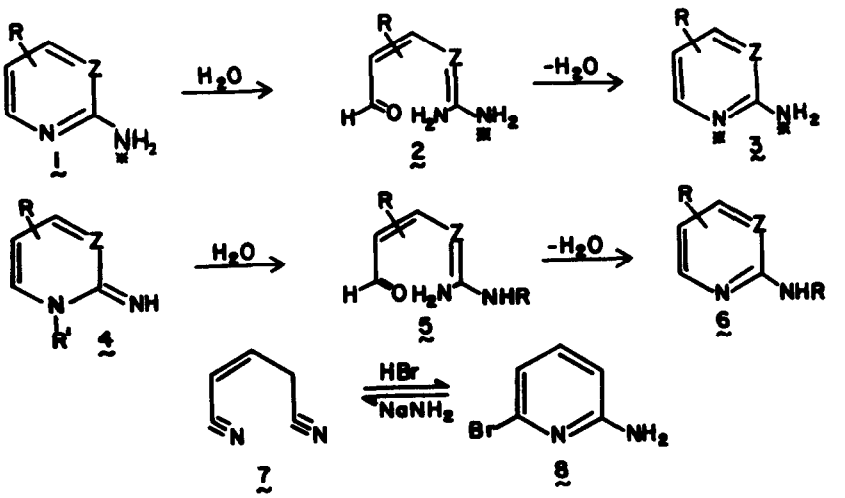
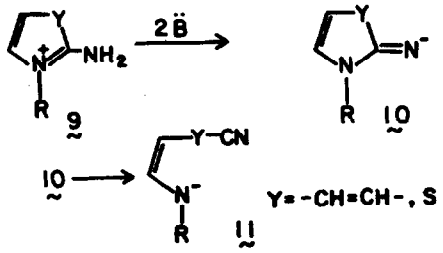
Abstract - 2-Amino-1-alkylpyridinium and 2-amino-3-alkylthiazolium cations are converted by n-BuLi into ω-aminopentadienenitriles and 2-alkylaminovinyl thiocyanates, respectively.

Ring-opening of α-amino-N-heterocycles after initial attack of a nucleophile at the α'-position is the first stage of the Dimroth rearrangement.[1] The Dimroth rearrangement of 2-aminopyridines (degenerate: demonstrated by ^{15}N-labelling)[2] (1 → 3, Z = CH), and of 1-alkyl-2-imino-1,2-dihydropyridines to 2-alkyliminopyrimidines[3] (4 → 6, Z = CH) require strongly electron withdrawing ring-substituents, e.g. R = 3- or 5-NO_2. For the 2-aminopyrimidine analogues[1] (1 → 3 or 4 → 6, Z = N) rearrangement occurs readily without such additional activation.

Pent-2-ene-1,5-dinitriles are cyclised in halogen acids to 2-aminopyridines,[4] thus glutaconononitrile 7 with HBr gives 2-amino-6-bromopyridine 8. Conversely 5% of glutaconononitrile was detected as a product of sodamide treatment of 2-amino-6-bromopyridine[5] (8 → 7). The mechanism of reaction 8 → 7 could involve either initial replacement of the 6-bromine or double deprotonation of the α-amino group of the 2-aminopyridine 8. The latter possibility would constitute a new type of ring-opening fundamentally different from the Dimroth rearrangement.



We now report definite examples of such ring-opening reactions of 2-amino-N-heterocycles in which 1-alkyl-2-aminothiazolium and pyridinium salts 9 and 12 give acyclic ω-alkylaminonitriles 11 or 13-16 by a ring-opening initiated by double deprotonation to 10.



Ring-Opening of 1-Alkyl-2-aminopyridinium Salts to 5-Alkylaminopentadienenitriles (Table 1). 2-Amino-1-methylpyridinium iodide 12a and its 3-, 4-, 5- and 6-methyl and 5-chloro substituted analogues 12b-f obtained by direct quaternisation of the corresponding pyridines, on treatment with n-butyl-lithium below 0 °C, all gave anions which immediately rearranged into substituted 5-methylamino-2,4-pentadienenitriles (52-74%) (Table 1). These nitriles were obtained as either single or mixed stereoisomers 13-15 (Scheme 1). 2-Amino-1-benzylpyridinium chloride 12g and its 4-methyl substituted analogue 12h witn n-butyl-lithium likewise underwent ring-opening to the substituted 5-benzylamino-2,4-pentadienenitriles 13g-h (70-90%) (Table 1) (Scheme 1).

These reactions 12 → 13-15 were accomplished by addition of n-butyl-lithium (2.2 equivalents) to a suspension of the pyridinium salt in THF at -78 °C, allowing the mixture to warm-up during 15 min, whereupon the pyridinium salt dissolved, and finally quenching with excess water below 0 °C, to inhibit polymerisation of the products. Work up at 25 °C throughout gave the 2-, 3-, 4- and 5-methyl substituted 5-methylaminopentadienenitriles solely as the 2Z,4Z isomers 13b-e, whilst the unsubstituted analogue was thus obtained as a mixture of isomers 13a, 14a and 15a, and the 4-chloro compound only as the 2E,4E isomer 15f (see discussion of spectra below). In most cases, heating these initial products briefly at 50-60 °C with LiOH caused isomerisation to mixtures containing roughly equal proportions of 2Z,4Z and 4Z,4E isomers, i.e. 14a and 15a; 14b and 15b, 14c and 15c. The 5-benzylaminopentadienenitriles were obtained only as the 2Z,4Z isomers 13g-h, which did not isomerise, probably due to electronic interaction between the phenyl ring and nitrile substituents.

The 1-methyl and 1-benzyl-2-aminothiazolium salts 17 and 18 also underwent ring-opening initiated by butyl-lithium deprotonation, giving the 2-alkylaminovinylthiocyanates 19 and 20.

Evidence for the 5-Alkylaminopentadienenitrile Structure and Stereochemistry of 13-15 (Tables 1-3).- The mass spectra of the 5-methylaminopentadienenitrile products 13c-f, 14a-b and 15a-b show the molecular ions as base peaks, whilst the 5-benzylamino analogues 13g-h give more intense $(M-1)^+$ peaks by facile loss of H· from M^+. High resolution m/e measurements of these M^+ ions give experimental molecular weights in excellent agreement with calculated values, (Table 1). This proves the molecular formulae for 13-15 which were obtained as oils and could not be satisfactorily microanalysed as they polymerised rapidly as bulk products even at 25 °C.

The i.r. spectra of 13-15 all showed strong ν C≡N 2185-2195 (Table 1), a weak ν N-H 3350-3450, and ν C=C at 1620-1650 cm^{-1}.

The ^1H n.m.r. spectra of the ω-alkylaminopentadienenitriles 13-15 (Tables 2 and 3) show 2-H and 4-H at relatively high field, δ4.4-6.4 and 5.2-5.8 respectively, due to

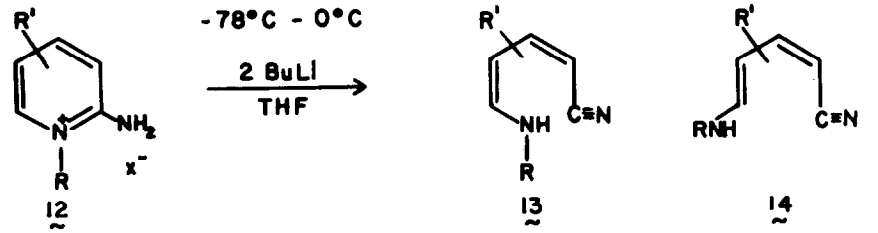
Table 1. Preparation of 5-Alkylaminopentadienenitriles 13 and 15, with Mass-spectral and I.r. Data.

Compound	N-Substituent R	Chain Substituent R'	Yield %	M^+ Found	Formula	M^+ Required	νC≡N cm^{-1}
14a,15a	Me	H	65	108.0686	$C_6H_8N_2$	108.0687	2192
14b,15b	Me	2-Me	52	122.0840	$C_7H_{10}N_2$	122.0844	2195
13c	Me	3-Me	63	122.0846	$C_7H_{10}N_2$	122.0844	2195
15f	Me	4-Cl	74	142.0290	$C_6H_7ClN_2$	142.0297	2195
13d	Me	4-Me	68	122.0844	$C_7H_{10}N_2$	122.0844	2185
13e	Me	5-Me	61	122.0851	$C_7H_{10}N_2$	122.0844	2190
13g	$PhCH_2$	H	70	184.0985	$C_{12}H_{12}N_2$	184.1000	2190
13h	$PhCH_2$	3-Me	90	198.1145	$C_{13}H_{14}N_2$	198.1156	2192

conjugation with the RNH substituent. Similar conjugation with the nitrile group causes 3-H and 5-H to appear at low field δ 6.5-6.9 and 6.6-7.0 respectively. In the compounds lacking extra substitution, a doublet is observed for 2-H, whilst 3-H and 4-H give triplets or double doublets, and 5-H a doublet, or double doublet if coupling to NH occurs. The presence of C-methyl substituent groups simplify these signals as expected.

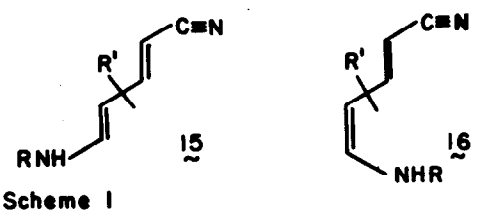
Stereochemical assignments are largely based on vicinal coupling constants. The 2Z,4Z dienes 13a-e and 13g-h show $J_{2,3}$ 9 Hz, with $J_{3,4}$ and $J_{4,5}$ 6.5-7 Hz, verified in 13g by double resonance decoupling. A low field resonance (δ6.05-6.35) for 2-H is also typical of the all Z-adducts, and was used to distinguish those (13b-e) where substitution precludes relevant information from coupling constants.

For the mixtures of unsubstituted 5-methylaminopentadienenitriles, the presence of both the 2Z,4E- 14a and 2E,4E-isomer 15a was fully established from homonuclear irradiation experiments at 300 MHz. Separate irradiation of the 9.5 Hz 2-H doublet in 14a, and the 14 Hz 2-H doublet in 15a decoupled the corresponding 3-H



12 13 14

	R	R'
a,	Me	H
b,	Me	2-Me
c,	Me	3-Me
d,	Me	4-Me
e,	Me	5-Me
f,	Me	4-Cl
g,	$PhCH_2$	H
h,	$PhCH_2$	3-Me



Scheme I

signals (originally double doublets) to simple doublets. The couplings $J_{3,4}$ 11.5 Hz and $J_{4,5}$ 13-13.5 Hz were similarly removed by irradiation of each of the 4-H signals, leaving the corresponding 3-H and 5-H signals as doublets, the latter due to coupling with NH ($J_{NH,5}$, 7 Hz). The other isomers 14b-d, 15b-d and 15f were assigned by analogy, however since full vicinal coupling information is not available, the possibility of 2E,4Z isomers 16d,f cannot be ruled out.

The off resonance ^{13}C n.m.r. spectra of the products 13-15 all showed typical signals for the five

Table 2. ^1H N.M.R. spectra of 2Z,4Z 5-Alkylaminopentadienenitriles[a] 13a-h

No.	13a	13b	13c	13d	13e	13g	13h
N-substituent R	Me	Me	Me	Me	Me	$PhCH_2$	$PhCH_2$
Chain Substituent, R'	H	2-Me	3-Me	4-Me	5-Me	H	3-Me
2-H	6.37	-	6.32	6.31	6.10	6.05	6.05
3-H	6.85	6.80	-	6.74	6.55	6.50	-
4-H	5.79	5.65	5.70	-	5.50	5.43	5.5
5-H	6.99	6.95	6.95	6.77	-	6.58	6.75
R(3H, s)	3.43	3.40	3.35	3.39	3.35	5.1[b]	5.0[b]
R'(3H, s)	-	1.95	2.10	1.93	2.15	-	1.95
$J_{2,3}$	9.5	-	-	9.5	9	9	-
$J_{2,4}$	-	-	2	-	-	1.5	2
$J_{3,4}$	7	7	-	-	6	6.5	-
$J_{4,5}$	7	7	7	-	-	6.5	7

Table 3. ^1H N.M.R. spectra[a] of 5-alkylaminopentadienenitriles 14a-c, 15a,c,d,f.

No.	14a	14b	14c	15a	15c	15d	15f
Stereochemistry	2Z,4E	2Z,4E	2E,4E	2E,4E	2E,4E	2E,4E	2E,4E
N-Substituent, R	Me	Me	Me	Me	Me	Me	Me
Chain Substituent R'	H	2-Me	3-Me	H	3-Me	4-Me	4-Cl
2-H	4.41	-	4.45	4.74	4.75	4.52	4.98
3-H	6.73	6.50	-	6.93	-	6.92	6.95
4-H	5.49	5.35	5.6	5.22	5.25	-	-
5-H	6.85[b]	6.70	6.9[b]	6.78[b]	6.95[b]	6.85	6.72
R(3H, s)	2.80[c]	2.70	2.75[d]	2.76[c]	2.8[d]	2.93	3.0
R'(3H, s)	-	1.90	1.95	-	2.1	1.56	-
$J_{2,3}$	9.5	-	-	14	-	16	14
$J_{2,4}$	-	-	-	-	-	-	-
$J_{3,4}$	11.5	12	-	11.5	-	-	-
$J_{4,5}$	13.5	13	13.5	13	14	-	-

[a] In $CDCl_3$, δ ppm $(CH_3)_4Si$ as internal reference. [b] $J_{NH;5}$ = 7 Hz. [c] J_{NH}, Me 3 Hz doublet. [d] J_{NH}, Me 2 Hz doublet.

Table 4. ^{13}C N.M.R. spectra of 5-Alkylaminopentadienenitriles 13-15

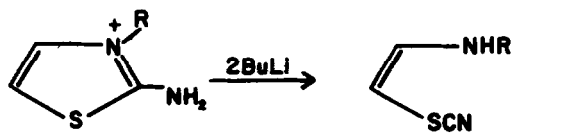
Compound	N-Substituent R	Chain Substituent R'	δc 1-C δ (s)	2-C δ	3-C δ	4-C δ	5-C δ	R δ	R' δ (q)
14a, 15a	Me	H	122.28 120.18	95.76d 95.42d	148.55d 148.30d	79.29d 81.00d	152.98d 151.86d	30.21q	-
14b, 15b	Me	2-Me	124.61 121.40	[b] [b]	146.35d 145.67d	94.88d 92.03d	147.62d 146.69d	30.06q	18.90
13c	Me	3-Me	105.72	113.08d	140.52s	100.92d	132.16d	33.93q	15.68
	Me	4-Cl	100.74	80.71d	143.84d	120.54s	145.84d	33.80q	-
15f	Me	4-Me	110.29	119.40d	134.22d	158.59s	136.17d	37.86q	15.79
13e	Me	5-Me	119.84	116.47d	134.16d	91.96d	153.71s	29.04q	17.00
13g	$PhCH_2$	H	135.48	120.18d	132.99d	101.85d	136.21d	51.89t	-
13h	$PhCH_2$	3-Me	137.26	118.50d	143.74s	104.46d	137.26d	51.09t	20.29

[a] Multiplicity indicated by: s, singlet; d, doublet; t, triplet; q, quartet.
[b] Obscured by overlap with other signals.

carbons of the pentadienenitrile backbone (Table 4). The nitrile carbon 1-C gives a singlet in all cases, at δ 100.7-124.6 in 13a-f, and at 135.5-137.3 in the 2Z,4Z-5-benzylamino-products 15, in which the proximity of the phenyl ring additionally deshields the nitrile carbon. The diene carbons 2-C, 3-C, 4-C and 5-C all give doublets, except when further substituted, when they give the expected singlets. The electronic effects of conjugation to the cyano or amino groups dominate the chemical shifts of the diene carbons in full agreement with the ^1H n.m.r. spectra. Thus 4-C, most conjugated with the amino group appears at highest field, δ 79.3-104.5, and 2-C, in weaker conjugation with NHR, and experiencing the inductive effect of α-CN, at 92.0-120.2 (ranges for =CH-carbons only). Carbons 3-C and 5-C are deshielded by conjugation with the nitrile group, and appear in the range δ 132.2-153.7: the relative assignment of 3-C and 5-C in Table 4 is arbitrary in many cases.

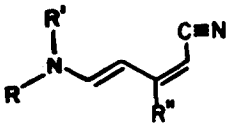
The N-methyl substituents in 13 give quartets at δ 29.0-37.9, the N-benzyl methylene groups in 15 triplets at δ 51.1-51.9, and the phenyl rings give doublets at δ 126.1-128.3 and a singlet at δ 158.7. The methyl chain substituents gave quartets at δ 15.7-20.3.

The 2-alkylaminovinylthiocyanates 19 and 20 showed νC≡N 2190, and νC=C 1640 cm^{-1}. The ^1H n.m.r. showed vinyl doublets at 5.7 and 6.4 p.p.m.: the off resonance ^{13}C n.m.r. spectra showed doublets for N-CH= at 136.2 20 or 128.3 19 and δ-CH= at 97.4, and a singlet for δCN at 164.7 p.p.m.

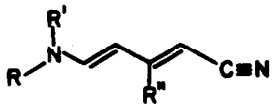


17 R=Me
18 R=CH_2Ph
19 R=Me
20 R=CH_2Ph

Similar Structures in the Literature.- 5-Dialkylamino-2,4-pentadienenitriles 21 have been prepared previously (i) by photolysis of pyridine N-oxides in the presence of dialkylamines, which add to the primary photoproducts 22[6] and (ii) by dehydration of the oximes 23.[7] Neither method approaches the preparative convenience and simplicity of that given above for compounds of type 13-15. Moreover, unlike in our method, where single 2Z,4Z isomers are often obtainable, the dimethylamino analogues are always obtained as mixtures 2E,4Z and 2E,4E isomers 21a and 21b.



21a



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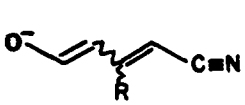

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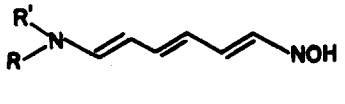

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In the previously reported 5-dimethylaminopentadienenitriles 21a and 21b, 1-C appeared at δ 127.4, 3-C at 147.7 and 5-C at 149.9, whilst 2-C and 4-C were assigned at 91.1 and 106.4 respectively (mean values). We prefer the converse assignment for 2-C and 4-C, as stated above but otherwise the values are in good general agreement with those for 13-15. The proton spectra for 21a and 21b gave mean δ values of 4.7 for 2-H, 5.4 for 4-H, 6.9 for 3-H and 6.7 for 5-H, again in general agreement with our values for 13-15.

EXPERIMENTAL

General Procedure for the Preparation of alkylaminopentadienenitriles and alkylaminovinyl thiocyanates.- The 2-aminopyridinium or thiazolium salt (2 mmol) as a suspension in THF (10 ml) at -78 °C under argon was treated with ^{n}BuLi in hexane (4.4 mmol). The mixture was allowed to warm to -0 °C, the orange/brown solution quenched with water (1.0 ml), and THF removed at 25 °C and 1 mmHg. The residue was washed with water (15 ml), extracted with CH_2Cl_2 (2 x 20 ml), and solvent removed at 20 °C and 1 mmHg, giving the ring opened products.

Instrumentation.- ^{1}H NMR (60 MHz): Varian A60A, ^{1}H NMR (300 MHz): Nicolet NT 300, and ^{13}C NMR (25.0 MHz): Jeol FX-100 spectrometers. MS:AEI MS30 spectrometer. IR (as a film on NaCl), Perkin Elmer 283B spectrophotometer.

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