Heterocycles of Biological Importance. Part 2. Novel Synthesis and Pharmacological Evaluation of 5-Amino-3-alkyl-1-(2-pyridyl)pyrazoles and 5-Amino-3-phenyl-1-(2-pyridyl)pyrazole from Allenic or Acetylenic Nitriles and 2-Hydrazinopyridine

Z. Tanee Fomum*

Department of Organic Chemistry, University of Yaounde,
B. P. 812, Yaounde, Cameroon

P. Ngozi Ifeadike

Department of Chemistry, University of Port Harcourt,
P. M. B. 5323, Port Harcourt, Nigeria

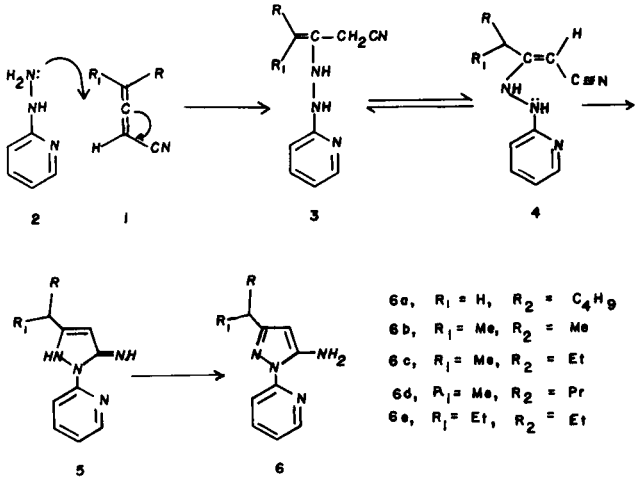
Received December 5, 1984

2-Hydrazinopyridine reacts with allenic and acetylenic nitriles to give 5-amino-3-alkyl-1-(2-pyridyl)pyrazoles **6** in excellent yields. One of these compounds, **6e** has been shown to possess anticonvulsant and anti-electroshock properties. Phenyl propynenitrile also reacts with hydrazinopyridine to give 5-amino-3-phenyl-1-(2-pyridyl)pyrazole (**11**) in quantitative yield.

J. Heterocyclic Chem., **22**, 1611 (1985).

We have already demonstrated the usefulness of allenic and acetylenic nitriles as starting materials for the synthesis of various heterocyclic compounds [2-8]. As a continuation of a recent study [1] of the synthesis of heterocycles of possible biological uses, we treated 2-hydrazinopyridine (**2**) with allenic nitriles **1** and found that they reacted either neat or in chloroform to give the 5-amino-3-alkyl-1-(2-pyridyl)imidazoles **6** in excellent yields (Scheme 1).

Scheme 1

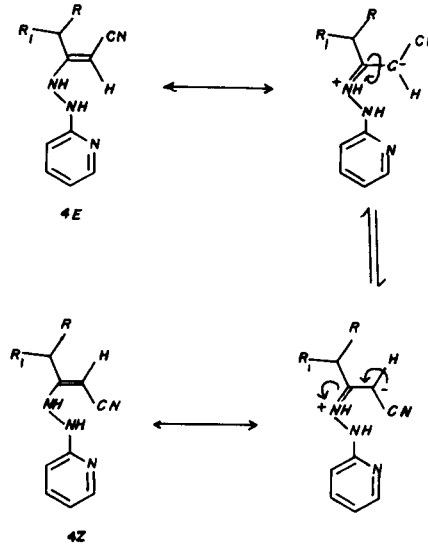


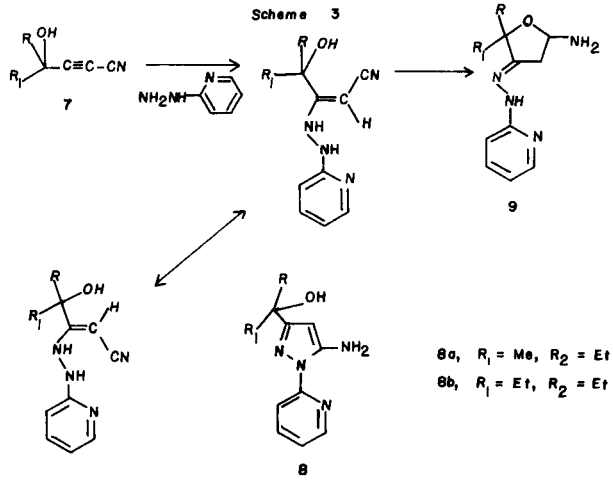
When the allenic nitriles and the 2-hydrazinopyridine were treated neat, exothermic reactions took place and the reactions were virtually complete within 2 minutes. However the high temperatures produced by the exothermic reactions caused polymerisation of the pyrazoles to about 20%. When the reactions were carried out under reflux in chloroform, cyclisation was complete in 3 hours and the crude products were obtained in quantitative yields of > 95% purity as shown by the nmr spectra.

The mechanism of formation of these aminopyridylpyrazoles involves a nucleophilic attack of the Michael carbon of the allenic nitrile by the amino function of the 2-hydrazinopyridine to give the unconjugated adduct **3** which isomerises to the conjugated adduct **4** [9] before cyclisation through the amino compound **5** to give the aminopyridylpyrazoles **6**.

It has clearly been demonstrated that enanimic nitriles exist as mixtures of the *E* and *Z* forms and that the *E* form predominates [10]. This form would disfavour cyclisation. The ready formation of these compounds can be explained by the existence of a labile equilibrium between the *E* and the *Z* form, the equilibrium shifting form the *E* to the *Z* form as cyclisation takes place (Scheme 2). The exothermic

Scheme 2

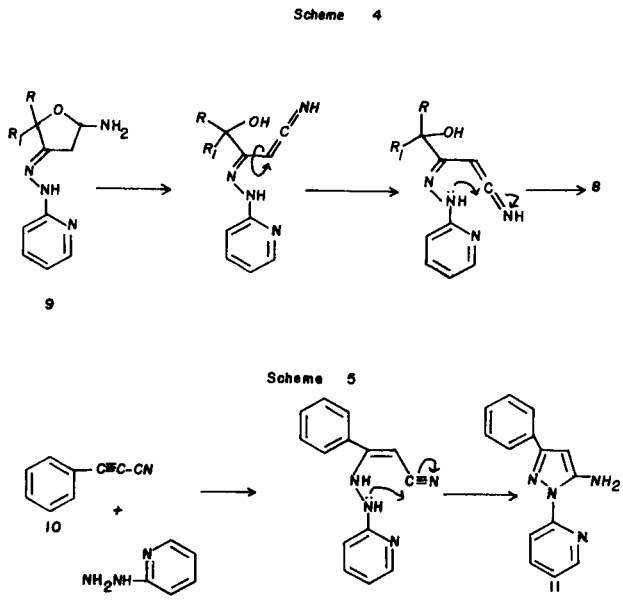




temperature of the reactions that were carried out neat and the reflux temperature of the ones in chloroform contribute to the conversion of the *E* to the *Z* isomers. When the reaction was carried out at 0°, the addition reaction was slow as well as the conversion of compound **3** to compound **4**. This permitted the detection of these intermediates. Cyclization was also slow further suggesting that high temperatures accelerate the conversion of the *E* to the *Z* form (Scheme 2).

Hydroxyacetylenic nitriles **7** react similarly with 2-hydrazinopyridine to give the corresponding aminohydroxypyridylpyrazoles **8**, in near quantitative yields, as the only product as shown by the nmr of spectra of the crude products (Scheme 3). It would have been expected that when this reaction was carried out at 0° in chloroform, formation of the aminofurans **9** [8] would take place in addition to the formation of the imidazoles **8**. The fact that the only product obtained is the imidazole can be explained on the basis that any aminofuran formed was readily converted into the pyrazole (Scheme 4).

Phenylpropynenitrile also reacts with hydrazinopyridine to give the 5-amino-3-phenyl-1-(2-pyridyl)pyrazole **11** in quantitative yield (Scheme 5).



A general screening of one of the 5-amino-3-alkylpyridylimidazoles **6e** for its effects on the central nervous system was carried out and the results are summarized in Table 3. It was found that this compound indicated anticonvulsion and antielectroshock properties. Further pharmacological analyses (Table 4) showed the magnitude of these properties in comparison with well known standards.

EXPERIMENTAL

The ir spectra were determined with a Perkin-Elmer 337 spectrophotometer. The uv spectra were obtained for ethanolic solutions with a Beckmann 25 spectrophotometer. The ^{1}H nmr spectra were determined with a Perkin-Elmer R 12A spectrophotometer for solutions in deuteriochloroform or otherwise stated with tetramethylsilane as the internal standard and are recorded as τ values. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. Allenic nitriles and 3-phenylpropynenitrile and hydroxyacetylenic nitriles were prepared as previously reported [12,13,14]. The melting points, uv spectra, analytical data and molecular ions data for the 5-amino-3-alkyl-1-(2-pyridyl)pyrazoles are given in Table 1. The ^{1}H nmr data are given in Table 2.

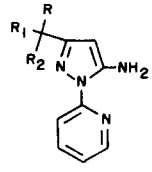
Table 1

Data of the 5-Amino-3-yl-1-(2-pyridyl)pyrazoles

Compound	λ max (nm)	ε × 10³	λ max (nm)	ε × 10³	Found C	H	N	Required C	H	N	M⁺
6a	254	14.8	280	9.1	66.61	7.53	25.78	66.67	7.41	25.92	216
6b	253	13.4	281	8.2	65.50	7.06	27.89	65.35	6.92	27.72	202
6c	254	14.1	282	8.6	66.81	7.31	26.08	66.67	7.41	25.92	216
6d	252	14.8	280	9.0	67.94	7.80	24.50	67.83	7.82	24.35	230
6e	253	15.2	280	9.2	67.75	7.89	24.30	67.83	7.82	24.35	230
9a	252	15.4	280	9.4	61.91	6.74	24.01	62.07	6.90	24.14	232
9b	252	16.0	280	9.50	63.28	7.21	22.91	63.91	7.32	22.76	246

Table 2

^{1}H NMR Data of 3-yl-1-(2-pyridyl)pyrazoles



	R	R_1	R_2	
6a	Bu	Me	H	9.10 (3H, t, $CH_3(CH_2)_3$), 8.85-8.05 (4H, m, $CH_3(CH_2)_2CH_2$), 7.50 (2H, t, $CH_3(CH_2)_2CH_2$), 4.68 (1H, s, $NH_2C=CH$), 4.12 (2H, s, NH_2, disappears on deuteriation), 3.20-2.90 (1H, m, N=C-CH=), 2.52-1.98 (2H, m, N-CH=CH-CH=), 1.90-1.67 (1H, m, N-CH=C)
6b	Me	Me	H	8.60 (6H, d, $(CH_3)_2CH$), 6.70-6.18 (1H, m, $(CH_3)_2CH$), 4.70 (1H, s, $NH_2C=CH$), 4.22 (2H, s, NH_2, disappears on deuteriation), 3.22-2.94 (1H, m, N=C-CH=), 2.56-2.00 (2H, m, N-CH=CH-CH=), 1.90-1.67 (1H, m, N-CH=C)
6c	Et	Me	H	9.10 (3H, t, $CH_3CH_2CHCH_3$, 8.80 (3H, d, $CH_3CH_2CHCH_3$), 8.72-8.00 (2H, m, $CH_3CH_2CHCH_3$), 7.70-7.10 (1H, m, $CH_3CH_2CHCH_3$), 4.73 (1H, s, $NH_2C=CH$) 4.30 (2H, s, NH_2, disappears on deuteriation), 3.20-2.90 (1H, m, N=C-CH=), 2.54-1.95 (2H, m, N-CH=CH-CH=), 1.90-1.65 (1H, m, N-CH=C)
6d	Pr	Me	H	9.10 (3H, t, $CH_3CH_2CH_2CHCH_3$, 8.86 (3H, d, $CH_3CH_2CH_2CHCH_3$), 8.80-8.15 (4H, m, $CH_3(CH_2)_2CHCH_3$), 7.79-7.25 (1H, m, $CH_3CH_2CH_2CHCH_3$), 4.75 (1H, s, $NH_2C=CH$), 4.28 (2H, s, NH_2, disappears on deuteriation), 3.25-2.95 (1H, m, N=C-CH=), 2.54-1.92 (2H, m, N-CH=CH-CH=), 1.90-1.68 (1H, m, N-CH=C)
6e	Et	Et	H	9.15 (6H, t, $(CH_3CH_2)_2CH$), 8.50 (4H, q, $(CH_3CH_2)_2CH$), 7.84-7.38 (1H, m, $(CH_3CH_2)_2CH$), 4.73 (1H, s, $NH_2C=CH$), 4.20 (2H, s, NH_2, disappears on deuteriation), 3.18-2.94 (1H, m, N=C-CH=), 2.50-1.96 (2H, m, N-CH=CH-CH=), 1.85-1.70 (1H, m, N-CH=)
9a	Et	Me	OH	9.12 (3H, t, $CH_3CH_2C(OH)CH_3$), 8.50 (3H, s, $CH_3CH_2C(OH)CH_3$), 8.20 (2H, q, $CH_3CH_2C(OH)$), 7.20 (1H, s, OH, disappears on deuteriation), 4.64 (1H, s, $NH_2C=C-CH$), 4.05 (2H, s, NH_2, disappears on deuteriation), 3.10-2.85 (1H, m, N=C-CH=), 2.45-1.90 (2H, m, N-CH=CH-CH=), 1.80-1.65 (1H, m, N-CH=C)
9b	Et	Et	OH	9.15 (6H, t, $(CH_3CH_2)_2$), 8.25 (4H, q, (CH_3CH_2C), 6.75 (1H, s, OH, disappears on deuteriation), 4.70 (1H, s, $NH_2C=CH$), 4.05 (2H, s, NH_2, disappears on deuteriation), 3.12-2.85 (1H, m, N=C-CH=), 2.47-1.95 (2H, m, N-CH=CH-CH=), 1.80-1.65 (1H, m, N-CH=C)

Table 3

Pharmacological Screening of Compound **6e**

1. Test	Route	Dose [a]	Criterion	Response
Toxicity	P.O [b]	300		No abnormal developments
Toxicity	I.P [c]	200		slight decrease in abdominal and limb tone
2. Antimetrazol	I.P	100	>3	6
3. Antielectroshock	P.O	100	<2	1
4. GABA [d] agonist	I.P	100	<3	3, 5

[a] Milligrams per kilogram of weight. [b] P.O = Par Os *i.e.* orally administered. [c] I.P = Intraperitoneally administered. [d] GABA = γ-amino-butyric acid.

Table 4

Further Tests on Compound **6e**

Test	Reference compound	Route	Dose	Response
2. Antimetrazol		P.O	300 mg/kg	4 MED [a]
Antimetrazol		P.O	100 mg/kg	2
Antimetrazol	meprobamate	P.O	200 mg/kg	5 ED 100 [b]
3. Antielectroshock		P.O	200 mg/kg	1 MED
		P.O	100 mg/kg	1
	meprobamate	P.O	100 mg/kg	0 ED 100
4. GABA Agonist		I.P	200 mg/kg	1,3 MED
		I.P	100 mg/kg	4,5
	sodium valproate	I.P	100 mg/kg	1,3 ED 100

[a] MED = Minimum effective dose. [b] ED 100 = Dose which is always active in test system.

5-Amino-3-pent-3-yl-1-(2-pyridyl)pyrazole (**6e**).

a) 4-Ethylhexa-2,3-dienenitrile (**1e**) (2.42 g, 20 mmoles) was added slowly to 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) and the mixture warmed for 5 minutes at 40°. An exothermic reaction took place, the temperature rising to 211°. The temperature was allowed to drop to room temperature and a dark brown oil was obtained in quantitative yield. Column chromatography (silcia gel), activity 5 and elution with chloroform-hexane (4:1) gave a solid (3.98 g) which was recrystallised from chloroform-hexane to give pure **6e** (3.6 g, 80%), mp 62°.

b) 4-Ethylhexa-2,3-dienenitrile (2.42 g, 20 mmoles) and 2-hydrazinopyridine (2.18 g, 20 mmoles) were dissolved in chloroform (50 ml) and the mixture refluxed for 12 hours, the course of the reaction being monitored by ir spectroscopy. The solvent was removed under reduced pressure and the residue allowed to stand overnight at 0° when it solidified and was recrystallised to give compounds **6e** in 90% yield.

c) 4-Ethylhexa-2,3-dienenitrile (2.42 g, 20 mmoles) and 2-hydrazinopyridine (2.18 g, 20 mmoles) were dissolved in chloroform (100 ml) and the mixture allowed to stand at 0° and the reaction monitored by ir spectra. After 48 hours, very little reaction had taken place, but after 14 days, the addition reaction was complete as shown by the disappearance of the allenic band at 1950 cm^{-1}. There was however strong absorption for the unconjugated nitrile (2220 cm^{-1}) of **3e** and the conjugated nitrile (2190 cm^{-1}) of **4e**. After 45 days cyclization was complete as indicated by the disappearance of the nitrile bands. Evaporation of solvent gave the crude product as an oil which solidified overnight to give the pyrazole **6e** in 85% yield.

5-Amino-3-(1-methylbut-3-yl)-1-(2-pyridyl)pyrazole (**6d**).

4-Methylhepta-2,3-dienenitrile (**1d**) (2.42 g, 20 mmoles) and 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) were dissolved in chloroform (70 ml) and refluxed for 15 hours. Removal of solvent followed by column chromatography (silcia gel, activity 5 and elution with chloroform-hexane (4:1) gave compound **6d** (4.05 g, 88%) as an oil.

5-Amino-3-(1-methylprop-3-yl)-1-(2-pyridyl)pyrazole (**6e**).

4-Methylhexa-2,3-dienenitrile (**1c**) (2.14 g, 2 mmoles) and 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) were treated similarly to give the pyrazole **6c** (3.5 g, 82%) as an oil.

5-Amino-3-isopropyl-1-(2-pyridyl)pyrazole (**6b**).

4-Methylpenta-2,3-dienenitrile (**1b**) (1.86 g, 20 mmoles) and 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) similarly gave the pyrazole **6b** (3.1 g, 77%) as an oil.

5-Amino-3-but-3-yl-1-(2-pyridyl)pyrazole (**6a**).

Hepta-2,3-dienenitrile (**1a**) (1.07 g, 10 mmoles) and 2-hydrazinopyridine **2** (1.09 g, 10 mmoles) similarly gave the pyrazole **6a** (1.8 g, 83%) as an oil.

5-Amino-3-(1-hydroxy-1-methylprop-3-yl)-1-(2-pyridyl)pyrazole (**9a**).

4-Hydroxy-4-methylhex-2-ynenitrile **7a** [14] (2.18 g, 20 mmoles) was added dropwise to 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) at 0°. The reaction mixture was kept at that temperature for 1 hour and then slowly allowed to warm up to room temperature. It was left overnight at room temperature when the crude product was obtained in quantitative yield. Column chromatography (silica gel, activity 5, elution with chloroform) gave the pyrazole **8a** (4.2 g, 90%) as an oil.

5-Amino-3-(1-hydroxyl-1-ethylpropyl)-3-yl-1-(2-pyridyl)pyrazole (**9b**).

4-Hydroxy-4-ethylhex-2-ynenitrile (1.37 g, 10 mmoles) and 2-hydrazinopyridine (1.09 g, 10 mmoles) were treated similarly to give the pyrazole **9b** (2.1 g, 86%) as an oil.

5-Amino-3-phenyl-3-yl-1-(2-pyridyl)pyrazole (**11**).

3-Phenylpropynenitrile **10** (2.54 g, 0.02 mole) and 2-hydrazinopyridine **2** (2.18 g, 20 mmoles) were dissolved in chloroform (100 ml) and refluxed for 12 hours. Removal of the chloroform yielded a solid which was recrystallised from chloroform-hexane to give the pyrazole **11** (4.3 g, 91%), mp 156°; ir (potassium bromide): ν max 3410, 3180 (NH_2); uv: λ max 208 (ϵ 15.3 × 10^3), 278 (ϵ 14.1 × 10^3), 290 (ϵ 13.0 × 10^3); nmr: 4.20 (1H, s, $NH_2C{=}CH$), 4.10 (2H, s, NH_2, disappears on deuteriation), 3.10-1.65 (9H, m, aromatic); ms: m/e 236 (M^+).

Biological Activity Tests.

Below are brief descriptions of the tests, explanation of the criterion and a listing of suitable reference compounds and their ED 100 (end result) value in mg/kg representing the dose which is always active in the test system rather than the minimal effective dose (MED) determined blind for test compound in a given dose response experiment. The experimental results are given in Tables 3 and 4.

Test 1. Acute toxicity. Mice were dosed at 300 mg/kg, p.o and 200 mg/kg, i.p for observation of any toxicity symptoms or autonomic effects during subsequent 72 hours.

Test 2. Antimetrazole. Two parameters were measured (prevention of death and prevention of convulsions). The first was scored 1 and the second given 2 points × 3 mice = 9 points possible. Scores greater than 3 denote anticonvulsant effect and peripherally mediated muscle relaxation. Mice were dosed with the test compound, p.o, three hours before injection of metrazol, 100 mg/kg, i.p, and scored during the subsequent 30 minutes: meprobamate (200), glutethimide (150).

Test 3. Antielectroshock. One hour after dosing mice, p.o, prevention of maximal electroshock seizures (MES) was determined. Appearance of MES extensor tonus in none or only one mouse (< 2) indicates antielectroshock activity: meprobamate (100), sodium valproate (400), acetazolamide (100).

Test 4. GABA agonist. Mice were dosed, i.p, followed 30 minutes and 5 hours later by two separate injections of bicuculline (0.5 mg/kg). Inhibition of convulsions [less than nice (< 3) exhibiting convulsions] after the first injection of bicuculline suggested direct GABA agonist activity whereas inhibition after the second injection may indicate inhibition of GABA - transaminase enzyme: sodium valproate (100), diphenylhydantoin (> 200).

Acknowledgement.

We thank the University of Yaounde Research Grants Committee for financial support and Mr. H. Mesi for technical assistance.

REFERENCES AND NOTES

[1] Part 1: Z. T. Fomum, P. F. Asobo and P. N. Ifeadike, *J. Heterocyclic Chem.*, **21**, 1125 (1984).

[2] Z. T. Fomum, P. D. Landor and S. R. Landor, *J. Chem. Soc., Chem. Commun.*, 706 (1974).

[3] Z. T. Fomum, P. D. Landor, S. R. Landor and G. W. B. Mpango, *Tetrahedron Letters*, 1101 (1975).

[4] S. R. Landor, P. D. Landor, Z. T. Fomum and G. W. B. Mpango, *Tetrahedron Letters*, 3743 (1977).

[5] Z. T. Fomum, J. T. Mbafor, S. R. Landor and P. D. Landor, *Tetrahedron Letters*, 4127 (1981).

[6] Z. T. Fomum, S. R. Landor, P. D. Landor and G. W. B. Mpango, *J. Chem. Soc., Perkin Trans. I*, 2997 (1981).

[7] S. R. Landor, P. D. Landor, Z. T. Fomum, J. T. Mbafor and A. E. Nkengfack, *J. Chem. Soc., Perkin Trans. I*, 1223 (1983).

[8] Z. T. Fomum, P. F. Asobo, S. R. Landor and P. D. Landor, *J. Chem. Soc., Chem. Commun.*, 1455 (1983).

[9] Z. T. Fomum, P. M. Greaves, P. D. Landor and S. R. Landor, *J. Chem. Soc., Perkin Trans. I*, 1108 (1973).

[10] Z. T. Fomum, J. T. Mbafor, S. R. Landor and P. D. Landor, *Tetrahedron*, in press (1984).

[11] P. F. Asobo, "Doctorat de Troisième Cycle" Thesis, University of Yaounde, 1983.

[12] P. M. Greaves, S. R. Landor and R. S. Laws, *J. Chem. Soc. (C)*, 291 (1968).

[13] S. R. Landor, P. D. Landor, Z. T. Fomum and G. W. B. Mpango, *J. Chem. Soc., Perkin Trans. I*, 2289 (1979).

[14] S. R. Landor, B. Dimitriou, R. Grezkowiak and D. F. Pavey, *J. Organomet. Chem.*, **93**, 129 (1975).

[15] Biological Activity tests were carried out by Panlabs, Taiwan.