

The Preparation of Some New 3- and 5-Amino-pyrazoles

by Endocyclic *N*-Substitution of

3(5)-Aminopyrazoles

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By reaction of some 4-carbethoxy(or cyano)-3(5)-*R*-5(3)-aminopyrazoles **1** with 2-nitrobenzoyl chloride or 2-nitrobenzenesulfonyl chloride, a number of novel 3- and 5-amino-1-(2-nitrobenzoyl or 2-nitrobenzenesulfonyl)pyrazoles **6** and **7** were obtained. Every compound appearing during the endocyclic *N*-substitution process can be identified and determined by glc. The use of nmr offers a rapid, unambiguous method for determining the proposed structures.

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A wide variety of pharmacological properties have been shown to be associated with pyrazole derivatives. A previous investigation has revealed that some 3-amino-4-carbethoxypyrazoles inhibited purine biosynthesis in a pigeon liver cell-free system (1). Recently, antibacterial activity of some 5-amino-4-cyanopyrazoles (2) has been reported.

Much of our work on the synthesis of heterocyclic compounds have been concerned with the study of reactions between some acylating agents and various amino-pyrazoles (3-6).

At this point it was desirable to explore the reaction of a number of 3(5)-aminopyrazoles bearing a carbethoxy or a cyano group at carbon 4 of type **1** with 2-nitrobenzoyl or 2-nitrobenzenesulfonyl chloride **2**, both from the point of view of production of compounds of biological importance and as an extension of our previous work designed to expand the chemistry of the pyrazole nucleus (7). In previous work (4) from this laboratory we have described the behaviour of some 3(5)-aminopyrazoles bearing an hydrogen atom at the 4-position or an alicyclic system fused at 3(5) and 4, towards condensation with 2-nitrobenzoyl chloride and we have found that they all lead to the

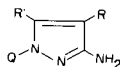
amides of type **3**.

We have observed that a variety of 4-carbethoxy(or cyano)-3(5)-aminopyrazoles **1** do not behave as typical aromatic amines towards 2-nitrobenzoyl chloride with formation of amides **3**. Instead their reactions are characteristic of the polarized form **4** and **5**. Electrophilic substitution occurs at the nitrogen atoms of the pyrazole nucleus with formation of 3- and 5-aminopyrazoles **6** and **7**.

In fact, the pyrazole **1** and acyl chloride **2** in chloroform in the presence of triethylamine afforded after refluxing, a reaction mixture, which gave two spots on tlc in chloroform:acetone 90:10. After separation as described in the experimental, the products were identified as 3- and 5-aminopyrazoles **6** and **7** by elemental and spectral analysis. Moreover, the isomers **7** were also prepared by condensation of the ethoxymethyleneacetates **8** and the appropriate hydrazides **9**. This synthetic approach employed to form **7** support the proposed structures. Both the isomers **6** and **7** exhibited two ir absorption bands at *ca* 3300 and 3400 cm^{-1} due to a typical primary amino group (see Table III). The nmr spectra showed chemical shift values for the substituent at carbon 3 or 5 and the amino group, which were of diagnostic value in distinguish-

Table I

1-Q-4,5-R,R'-3-Aminopyrazole Derivatives



Compound	R	R'	Q	Mp°	Formula	Analyses					
						Calcd.		Found			
						C	H	N	C	H	N
6a	COOC ₂ H ₅	H	2-NO ₂ -C ₆ H ₄ -SO ₂	160-162	C ₁₂ H ₁₂ N ₄ O ₆ S	42.36	3.56	16.47	42.47	3.64	16.40
6b	COOC ₂ H ₅	H	2-NO ₂ -C ₆ H ₄ -CO	170-172	C ₁₃ H ₁₂ N ₄ O ₅	51.31	3.98	18.42	51.41	4.14	18.47
6c	CN	H	2-NO ₂ -C ₆ H ₄ -CO	193-195	C ₁₁ H ₇ N ₅ O ₃	51.36	2.74	27.23	51.52	2.88	27.30
6d	COOC ₂ H ₅	CH ₃	2-NO ₂ -C ₆ H ₄ -CO	136-138	C ₁₄ H ₁₄ N ₄ O ₅	52.83	4.43	17.60	52.87	4.42	17.74
6e	CN	CH ₃	2-NO ₂ -C ₆ H ₄ -CO	285-287	C ₁₂ H ₉ N ₅ O ₃	53.14	3.34	25.82	53.24	3.27	25.79

All the products were recrystallized from ethanol.

ishing between the two isomers **6** and **7**.

In fact, the resonance band of the amino group of the 3-aminopyrazoles **6** has been observed at higher field (*ca* 1 ppm) with respect to the shift of the amino group of the 5-aminopyrazoles **7**, meanwhile the resonances of the hydrogen or the methyl group at C-5 of the isomers **6** appeared at lower field (*ca* 1 ppm) with respect to the shift of the hydrogen or methyl group at C-3 of isomers **7** (see Table III).

A rapid method was needed to follow the *N*-substitution of 3(5)-aminopyrazoles **1** to enable determination of quantities of isomers as well as other undesirable by-products.

Gas chromatography was selected as a reasonable approach. Quantitative analysis was readily accomplished by calibrating the recorder response in terms of a known amount of pure standards **6** and **7**.

Recognition of dienamine **4** behaviour for the carboethoxy or cyano-3(5)-aminopyrazoles **1**, proved of considerable value to the synthetic chemistry; this observation should also contribute a convenient procedure for the preparation of novel substituted 1-(2-nitrobenzoyl or benzenesulfonyl)-4-carboethoxy(or cyano)-3-aminopyrazoles **6**.

EXPERIMENTAL

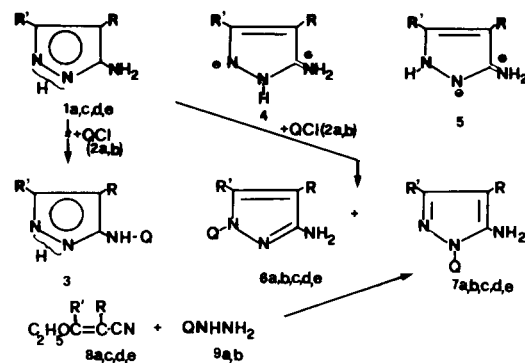
The melting points were determined on Buchi-Tottoli apparatus and are uncorrected. The ir spectra were determined in nujol mulls with a Perkin-Elmer 299 spectrophotometer. The nmr spectra were obtained with a Varian EM-360 60 MHz spectrometer (TMS as the internal reference).

The glc analyses were performed on a Varian gas chromatography Model 3700, with a flame ionization detector. The glass column was maintained at approximately 220°. The preheater (injection port) and exit line were operated at about 250°. The column was 2 meters in length and 2 mmeters in inner diameter. The column used was packed with Chromosorb W-HP 80 to 100 mesh loaded to 3% weight with OV 101. Nitrogen was used as the carrier gas.

Reaction of 3(5)-Aminopyrazoles **1** with Acyl Chloride **2**.

General Procedure.

A mixture of 3(5),4-disubstituted-5(3)-aminopyrazoles **1a** (**8**), **c** (**9**), **d**



a	R=COOC ₂ H ₅	R'=H	Q=2-NO ₂ -C ₆ H ₄ -SO ₂
b	R=COOC ₂ H ₅	R'=H	Q=2-NO ₂ -C ₆ H ₄ -CO-
c	R=CN	R'=H	Q=2-NO ₂ -C ₆ H ₄ -CO-
d	R=COOC ₂ H ₅	R'=CH ₃	Q=2-NO ₂ -C ₆ H ₄ -CO-
e	R=CN	R'=CH ₃	Q=2-NO ₂ -C ₆ H ₄ -CO-

(**10**), **e** (**11**) (10 mmoles) and acyl chloride **2a, b** (10 mmoles) was heated under reflux in dry chloroform (100 ml) in the presence of triethylamine (1.1 ml) for three hours. Excess solvent was removed under reduced pressure and the residue was mixed with water. The resulting solid material was filtered off and air dried. The crude reaction mixture gave two spots on tlc on silica gel in chloroform:acetone 90:10.

1-(2-Nitrobenzenesulfonyl)-4-carboethoxy-3-aminopyrazole (**6a**) and 1-(2-Nitrobenzenesulfonyl)-4-carboethoxy-5-aminopyrazole (**7a**), 1-(2-Nitrobenzoyl)-4-carboethoxy-3-aminopyrazole (**6b**) and 1-(2-Nitrobenzoyl)-4-carboethoxy-5-aminopyrazole (**7b**).

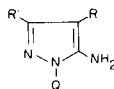
The crude solid was dissolved in boiling ethanol. Upon cooling to room temperature the crystals formed were collected and washed with ethanol to give **6a, b**. The mother liquors were concentrated until little volume to leave **7a, b**. The isomeric pyrazoles listed in Tables I and II were obtained in ratios reported in Table IV in 88-90% overall yield.

1-(2-Nitrobenzoyl)-4-cyan-3-aminopyrazole (**6c**) and 1-(2-Nitrobenzoyl)-4-cyan-5-aminopyrazole (**7c**).

The crude solid was washed with chloroform at room temperature. The insoluble material was filtered off and was identified as **6c**. Upon evaporation of chloroform **7c** was obtained. The isomeric pyrazoles listed in Tables I and II were obtained in 90% overall yield.

Table II

1-Q-3,4-R',R-5-Aminopyrazole Derivatives.



Compound	R	R'	Q	Mp°	Formula	Analyses					
						Calcd.	Found	Calcd.	Found		
						C	H	N	C	H	N
7a	COOC ₂ H ₅	H	2-NO ₂ -C ₆ H ₄ -SO ₂	108-115	C ₁₂ H ₁₂ N ₄ O ₆ S	42.36	3.56	16.47	42.45	3.57	16.44
7b	COOC ₂ H ₅	H	2-NO ₂ -C ₆ H ₄ -CO	138-140	C ₁₃ H ₁₂ N ₄ O ₅	51.33	3.98	18.42	51.44	3.92	18.43
7c	CN	H	2-NO ₂ -C ₆ H ₄ -CO	239-242	C ₁₀ H ₇ N ₅ O ₃	51.36	2.74	27.23	51.27	2.86	27.13
7d	COOC ₂ H ₅	CH ₃	2-NO ₂ -C ₆ H ₄ -CO	124-126	C ₁₄ H ₁₄ N ₄ O ₅	52.83	4.43	17.60	52.89	4.56	17.57
7e	CN	CH ₃	2-NO ₂ -C ₆ H ₄ -CO	256-258	C ₁₂ H ₈ N ₅ O ₃	53.14	3.34	25.82	53.26	3.28	25.80

All the products were recrystallized from ethanol.

Table III

Characteristic NMR and IR Data of Compounds **6** and **7**

Compound	NMR (DMSO-d ₆ , δ -values from TMS)		IR (cm ⁻¹ , Nujol)	
	R'	NH ₂	ν NH ₂	
6a	8.48 (H)	6.50	3380	3500
6b	8.80 (H)	6.10	3300	3440
6c	9.30 (H)	6.40	3300	3450
6d	2.90 (CH ₃)	5.90	3340	3440
6e	2.75 (CH ₃)	6.30	3360	3420
7a	8.00 (H)	7.20	3360	3480
7b	7.40-8.50 (a)		3320	3480
7c	7.70-8.70 (a)		3300	3440
7d	2.10 (CH ₃)	7.65	3300	3440
7e	2.00 (CH ₃)	7.80-8.50 (a)	3300	3440

(a) The H and/or NH₂ resonance bands were overlapped by aromatic protons signals

Table IV

Compound	Retention time		Retention		Yield	
	T _R		Mm* (a)		%	
	6	7	6	7	6	7
a	13'18"	11'21"	66.5	56.8	80.50	19.50
b	14'24"	12'24"	72	62	90.10	9.89
d	17'0"	13'34"	85	67.9	22.09	77.90
e	13'30"	12'26"	67.5	62.2	66.66	33.33

Compounds **6c** and **7c** showed the same T_R. No separation.

(a) Chart speed = 5 mm/minutes. Flow rate = 30 cc/minutes.

1-(2-Nitrobenzoyl)-4-carbomethoxy-5-methyl-3-aminopyrazole (**6d**) and 1-(2-Nitrobenzoyl)-4-carbomethoxy-3-methyl-5-aminopyrazole (**7d**).

The products were separated by preparative tlc on silica gel using chloroform:acetone as eluent. The isomeric pyrazoles listed in Tables I and II were obtained in ratios reported in Table IV in 78% overall yield.

1-(2-Nitrobenzoyl)-4-cyan-5-methyl-3-aminopyrazole (**6e**) and 1-(2-Nitrobenzoyl)-4-cyan-3-methyl-5-aminopyrazole (**7e**).

The crude solid was washed with methanol at room temperature. The insoluble material was filtered off and was identified as **7e**. Upon evaporation of methanol **6e** was obtained. The isomeric pyrazoles listed in Tables I and II were obtained in ratios reported in Table IV in 80% overall yield.

Reaction of Ethylethoxymethylcyanacetates **8** with Hydrazide Derivatives **9**.

To a solution of **8a** (**8**), **c** (**12**), **d** (**10**), **e** (**11**) (10 mmoles) and **9a** (**13**), **b** (**13**) (10 mmoles) dissolved in ethanol at room temperature, a few drops of acetic acid were added and then the mixture was allowed to stand overnight at the same temperature. The crystals thus formed were collected and recrystallized from ethanol to give products **7** identical in all respects with the 5-aminopyrazole derivatives obtained as above described (yield 70-75%).

In the case of **1d**, a solid precipitated (**14**), which was refluxed for 1 hour in ethanol to give quantitatively **7d**.

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- (14) This product, which was not identified, showed an ir absorption band characteristic of a C≡N group at 2220 cm⁻¹. Likely, it was the intermediate ethyl α -cyano- β -(2-nitrobenzoyl)hydrazinocrotonate, precursor of **7d**.