Selective Method for the Preparation of Isomeric *N*-Alkyl and *N*-Aryl-3(5)-amino-5(3)-hydroxy-1*H*-pyrazole-1-carboxamides

James T. Drummond and Graham Johnson*

Parke-Davis Pharmaceutical Research Division,
Warner-Lambert Company
Ann Arbor, Michigan, 48105

Received December 8, 1987

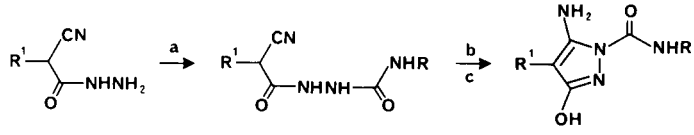
As part of a program to develop novel mechanism based skeletal muscle relaxants we identified 5-amino-3-hydroxy-1*H*-pyrazole-1-carboxamide (**1**) as a potential structural lead. This highly functionalized pyrazole was prepared *via* a published procedure [1] (Scheme 1, R = R' = H), which utilized 3,5-dimethyl-1*H*-pyrazole-1-carboxamide as an aminocarbonyl transfer reagent, to give with cyanoacethydrazide the semicarbazide intermediate **6**. Base catalyzed cyclization of **6** afforded the initial lead compound. This reaction scheme was extended to the synthesis of additional 4-alkyl- and 4-aryl-5-amino-3-hydroxy-1*H*-pyrazole-1-carboxamides (Table 1).

J. Heterocyclic Chem., **25**, 1123 (1988).

With the objective of synthesizing an extended series of *N*-alkyl and *N*-aryl-5-amino-3-hydroxy-1*H*-pyrazole-1-carboxamide analogs, the reaction of 3-amino-1*H*-pyrazol-5-ol (**7**) with a range of alkyl and aryl isocyanates was investigated as a more direct route to the desired analogs than that shown in Scheme 1. Treatment of **7** with phenyl isocyanate at room temperature (Scheme 2, R = Ph) gave two products. Extraction with refluxing ethyl acetate removed the minor component leaving the major as an insoluble crystalline solid. On cooling, the minor component separated out as a crystalline solid. That both products had been formed by the addition of isocyanate to each pyrazole ring nitrogen was confirmed by elemental analysis and NMR.

To confirm that the major product from this reaction was the expected 5-amino-3-hydroxy-*N*-phenyl-1*H*-pyrazole-1-carboxamide (**10**) it was compared with material synthesized previously by the route outlined in Scheme 1. Surprisingly, comparison of spectral data indicated that the isolated major product was in fact not **10** but the isomeric 3-amino-5-hydroxy-*N*-phenyl-1*H*-pyrazole-1-carboxamide (**13**) [2].

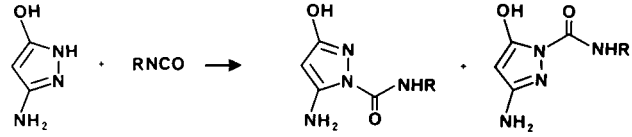
Scheme 1



6 (R = R' = H)

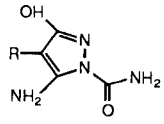
a = 3,5-dimethyl-1*H*-pyrazole-1-carboxamide or RNCO, b = 2*N* NaOH, c = H_3O^+

Scheme 2



7

Table 1



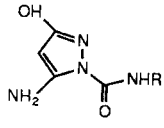
R	Compound	Hydrazide Yield %	Compound	Semicarbazide Yield %	Semicarbazide mp	Compound	Pyrazole Yield %	Pyrazole mp
H		–	**22**	74	194-195° [a]	**1**	57	159-160°
Et [5]	**18**	61	**23**	23	152-153°	**2**	35	155-157°
Octyl	**19**	73	**24**	36	130-133°	**3**	50	118°
Ph [5]	**20**	79	**25**	59	178-182°	**4**	57	163-164°
$(Ph)_2CH$	**21**	50	**26**	52	176-177°	**5**	51	134-135°

[a]Literature [1] mp 190°.

Since the originally isolated product had been subjected to refluxing ethyl acetate, the possibility that a thermal interconversion of **10** to **13** had occurred to alter the relative yields was investigated. Treatment of **10** in refluxing ethyl acetate was found to afford a clean interconversion of **10** to its much less soluble isomer **13** [3]. The interconversion of **10** to **13** was also seen to occur in the absence of solvent. Heating **10** to its melting point was followed by resolidification to give **13** as a higher melting product.

The migration of a subtituted amino carbonyl group is presumed to involve the transient regeneration of an isocyanate [4] followed by readdition to either pyrazole nitrogen. The ease of aminocarbonyl migration was noted to be dependent on the nature of the substituent group and to be in the order aryl > alkyl > H and hence may be related to the acidity of the proton attached to amino carbonyl group and its ease of abstraction by the adjacent amino group (Scheme 2) and/or the stability of the regenerated isocyanate. Indeed, the observed rate for the rearrangement of 5-amino-3-hydroxy-1*H*-pyrazole-1-carboxamide (**1**) to its isomer **17** (Table 3) was too slow to be preparatively useful. Compound **17** was synthesized more effectively by the reaction of 3-amino-1*H*-pyrazol-5-ol (**7**) with 3,5-dimethyl-1*H*-pyrazole-1-carboxamide as described above.

Table 2

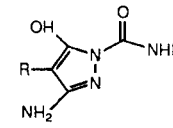


R	Compound	Semicarbazide Yield %	mp	Compound	Pyrazole Yield %	mp
CH_3	**27**	91	195-197°	**8**	48	168-169°
CH_2CH_2Cl	**28**	92	166-167°	**9**	73	160°
Ph	**29**	80	178-180°	**10**	63	195-196°
2,6-$(Et)_2$PH	**30**	93	216°	**11**	45	128-129°
4-(PhO)Ph	**31**	96	196-197°	**12**	92	179-181°

The ability to synthesize selected pyrazole isomers was further demonstrated by the extension of the reactions described above to generation of a small series of new *N*-alkyl and *N*-aryl substituted 5-amino-3-hydroxy-1*H*-pyrazole-1-carboxamides (Table 2) and their 3-amino-5-hydroxy isomers (Table 3).

The complementary synthetic methods outlined above should allow for the ready synthesis of a variety of new and highly substituted pyrazoles.

Table 3



Compound	R^1	R	Route/Solvent	Yield	Melting Point
13	H	Ph	A / EtOAc	47% [a]	207-209°
14	H	2,6-$(Et)_2$Ph	A / EtOAc	64%	160-161°
15	H	4-(PhO)Ph	A / EtOAc	80%	194-195°
16	Ph [b]	Ph	A / THF	47%	245-246°
17	H	H	B	–	180°

[a] Yield after brief treatment in refluxing ethyl acetate, equivalent to a 74% yield based on recovered starting material. [b] Precursor **33** was prepared in crude quantitative yield by the route shown in Scheme 1 and isolated as an analytically pure solid following chromatography (mp 245-246°). Route A Thermal rearrangement of 5-amino-3-hydroxy isomer. Route B Direct addition of 3,5-dimethyl-1*H*-pyrazole-1-carboxamide to 5-amino-3-hydroxy-1*H*-pyrazole.

EXPERIMENTAL

Melting points (uncorrected) were obtained using a Thomas Hoover capillary melting point apparatus. The ^{1}H nmr spectra were obtained on a Varian Associates EM-390, a Varian Associates XL-200 (200 MHz) or a IBM WP100SY (100 MHz) spectrometer. The nmr solvents are indicated under individual compound entries. The ir spectra were acquired on a Nicolet MX-1 FTIR. Elemental analyses were within 0.4% of calculated [8].

General Procedure for the Reaction of α-Cyanoacetates with Hydrazine [5].

Hydrazine monohydrate (4.1 g, 74 mmoles) was added dropwise to a solution of ethyl α-cyanobenzeneacetate (14.0 g, 74 mmoles) in absolute ethanol (75 ml). The reaction was stirred overnight at room temperature as a precipitate slowly formed which was filtered and washed with a small amount of cold ethanol to give α-cyanobenzeneacetic acid hydrazide (**20**) (8.9 g, 68% yield) mp 110°, (lit 110-111° [5]). Additional material could be isolated by concentration of the filtrate. By a similar procedure **18** [5], **19** and **21** were isolated in 61, 73 and 50% yield respectively.

α-Cyanononanoic Acid Hydrazide **19**.

This compound was obtained as a white solid, mp 78-79° (ethanol); ir (potassium bromide): 3307 (s), 2920 (s), 2255 (w), 1654 (s), 1623 (m), 1536 (m) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ ppm 7.7 (bs, 1), 3.85 (bs, 2), 3.3 (t, 1), 1.9 (m, 2), 1.3 (bs, 12), 0.8 (t, 3).

Anal. Calcd. for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.89. Found: C, 62.44; H, 9.89; N, 19.91.

α-Cyano-3,3-diphenylpropionic Acid Hydrazide **21**.

This compound was obtained as a white solid, mp 158° (ethanol): ir (potassium bromide): 3300 (broad), 2247 (w), 1659 (m), 1620 (m), 749 (m), 704 (s) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ ppm 9.4 (bs, 1), 7.1-7.4 (m, 10), 4.6 (d of d, 2), 4.3 (bs, 2).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.54; H, 5.50; N, 15.88.

General Procedure For The Reaction of The Hydrazides **18-21** with 3,5-Dimethyl-1*H*-pyrazole-1-carboxamide.

α-Cyanobenzeneacetic acid hydrazide (8.8 g, 50.3 mmoles) was dissolved in absolute ethanol (100 ml) and 3,5-dimethyl-1*H*-pyrazole-1-carboxamide (8.8 g, 63.3 mmoles) was added in one portion. The solution was warmed 30 minutes on a steam bath, allowed to cool to room temperature then filtered to give α-cyanobenzeneacetic acid 2-(aminocarbonyl) hydrazide **(25)** (4.57 g). On standing an additional 1.9 g of analytical product separated (6.5 g total, 59% yield). Also prepared by this method were **22**, **23**, **24** and **26** in 74, 23, 36 and 52% yield respectively.

α-Cyanobenzeneacetic Acid 2-(Aminocarbonyl) Hydrazide **25**.

This compound was obtained as a white crystalline solid, mp 178-182° (ethanol); ir (potassium bromide): 3448 (m), 3360 (br), 3200 (br), 2258 (w), 1686 (s), 1646 (s), 1567 (s), 702 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm 10.1 (bs, 1), [7.9, 8.0] (bs, 1), 7.0-7.5 (m, 5), 6.4 (bs, 1), 5.9 (bs, 1), 5.0 (s, 1).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.67. Found: C, 55.07; H, 4.79; N, 25.75.

α-Cyanobutyric Acid 2-(Aminocarbonyl) Hydrazide **23**.

This compound was obtained as a crystalline solid, mp 152-153°; ir (potassium bromide): 3502 (m), 3397 (m), 3220 (broad), 2252 (w), 1714 (s), 1669 (s), 1578 (m), 1534 (m) cm^{-1}; ^1H nmr in (DMSO-d_6): [7] δ ppm [9.8, 9.3] (bs, 1), [7.9, 8.1] (bs, 1), [5.9, 6.1] (bs, 2), 3.6 (t, 1), 1.8 (quint, 2), 1.0 (t, 1).

Anal. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.05; H, 5.86; N, 32.90.

α-Cyanononanoic Acid 2-(Aminocarbonyl) Hydrazide **24**.

This compound was obtained as a crystalline solid, mp 130-133°; ir (potassium bromide): 3498 (m), 3394 (m), 3230 (broad), 2250 (w), 1715 (s), 1669 (s), 1579 (m), 1533 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [9.9, 9.4] (s, 1), [7.9, 8.1] (s, 1), [6.0, 6.2] (s, 2), 3.6 (t, 1), 1.8 (m, 2), 1.3 (bs, 12), 0.8 (t, 3).

Anal. Calcd. for $C_{12}H_{22}N_4O_2$: C, 56.67; H, 8.72; N, 22.03. Found: C, 56.68; H, 9.06; N, 21.80.

α-Cyano-3,3-diphenylpropionic Acid 2-(Aminocarbonyl) Hydrazide **26**.

This compound was obtained as a crystalline solid, mp 176-177° (ethanol); ir (potassium bromide): 3461 (m), 3120-3300 (broad), 2249 (w), 1700 (s), 1686 (s), 1497 (m), 1599 (m), 1453 (m), 706 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [10.1, 9.4] (d, 1), [8.0, 8.2] (d, 1), 7.3 (m, 10), 5.5 (bs, 2), 4.6 (s, 2).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 65.92; H, 5.24; N, 18.23.

General Procedure For The Reaction of α-Cyanoacetic Acid Hydrazide with Alkyl and Aryl Isocyanates [6].

Cyanoacetic acid hydrazide (3.5 g, 35.4 mmoles) was suspended in acetonitrile (70 ml). With mechanical stirring a solution of 2,6-diethylphenylisocyanate (6.2 g, 35.4 mmoles) in acetonitrile (10 ml) was added dropwise. A thick precipitate formed and the reaction was diluted with acetonitrile (30 ml) to aid stirring. The reaction was stirred 45 minutes, filtered and washed with acetonitrile (75 ml). The solid was dried overnight at 60° *in vacuo* to afford cyanoacetic acid 2-[[(2,6-diethylphenyl)-amino]carbonyl] hydrazide **30** (9.0 g, 93% yield). Also prepared by this method were **27**, **28**, **29**, **31** and **32** in 91, 92, 80, 96 and 86% yield respectively.

α-Cyanoacetic Acid 2-(2,6-Diethylphenylaminocarbonyl) Hydrazide **30**.

This compound was obtained as a white solid, mp 216° (acetonitrile); ir (potassium bromide): 3320 (s) (broad), 2266 (w), 1709 (s), 1655 (s), 1537 (m) (broad), 1232 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [10.1, 9.5] (bs, 1), [8.2, 8.3] (bs, 1), 8.0 (s, 1), 7.0-7.2 (m, 3), [3.65, 3.7] (s, 2), 2.5 (q, 4), 1.1 (t, 6).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.43. Found: C, 61.51; H, 6.61; N, 20.54.

α-Cyanoacetic Acid 2-(Methylaminocarbonyl) Hydrazide **27**.

This compound was obtained as an off-white powder, mp 195-197° (acetonitrile); ir (potassium bromide): 3365 (s), 3200 (m), 3014 (m), 2259 (w), 1668 (s), 1577 (s), 1548 (m), 948 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [9.8, 9.4] (bs, 1), [7.9, 8.1] (s, 1), [6.4, 6.5] (q, 1), [3.6, 3.7] (s, 2), 2.5 (d, 2).

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.34; H, 5.14; N, 35.95.

α-Cyanoacetic Acid 2-(2-Chloroethylaminocarbonyl) Hydrazide **28**.

This compound was obtained as an off-white powder, mp 166-167° (acetonitrile); ir (potassium bromide): 3368 (m), 3240 (m), 3030 (m), 2270 (w), 1721 (w), 1675 (s), 1563 (s), 956 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [9.9, 9.4] (bs, 1), [8.1, 8.2] (s, 1), [6.7, 7.0] (t, 1), 3.6 (t, 2), 3.5 (t, 2), 3.3 (s, 2).

Anal. Calcd. for $C_6H_9ClN_4O_2$: C, 35.22; H, 4.43; N, 27.38. Found: C, 35.37; H, 4.43; N, 27.30.

αCyanoacetic Acid 2-(Phenylaminocarbonyi) Hydrazide **29**.

This compound was obtained as an off-white solid, mp 178-180° (acetonitrile); ir (potassium bromide): 3343 (w), 3240 (broad), 2260 (w), 1679, 1627, 1601 (s), 1556 (s), 939 (m), 757 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [9.9, 9.4] (bs, 1), [8.6, 8.9] (bs, 1), [8.1, 8.2] (bs, 1), 6.8-7.4 (m, 5), 3.6 (s, 2), 3.65 (s, 2).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.01; H, 4.62; N, 25.85.

α-Cyanoacetic Acid 2-(4-Phenoxyphenylaminocarbonyl) Hydrazide **31**.

This compound was obtained as a white powder, mp 196-197°; ir (potassium bromide): 3300 (broad), 2264 (w), 1694 (s), 1663 (s), 1491 (s), 1508 (s), 1229 (s) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [10.0, 9.5] (s, 1), [8.8, 9.0] (s, 1), [8.25, 8.3] (s, 1), 7.3-7.5 (m, 4), 6.9-7.1 (m, 5), [3.7, 3.75] (s, 2).

Anal. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 62.07; H, 4.62; N, 18.06.

α-Cyanobenzeneacetic Acid 2-(Phenylaminocarbonyl) Hydrazide **32**.

This compound was obtained as a white solid, mp 235°; ir (potassium bromide): 2900-3500 (broad), 2255 (w), 1698 (s), 1600 (s), 1560 (s), 1225 (s), 753 (m), 694 (m) cm^{-1}; ^1H nmr (DMSO-d_6): [7] δ ppm [10.3, 11.1] (bs, 1), 8.8 (s, 1), 8.3 (s, 1), 6.7-7.6 (m, 10), 5.1 (s, 1).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.09; H, 4.80; N, 19.25.

General Procedure for the Cyclization of The Semicarbazides **22-32**.

Cyanoacetic acid 2-[[2,6-diethylphenyl)amino]carbonyl] hydrazide (5.0 g, 18.2 mmoles) was dissolved in 2*N* sodium hydroxide (20 ml) plus water (10 ml) and stirred at room temperature for 40 minutes then acidified slowly with 2*N* hydrochloric acid (20 ml). To maintain efficient stirring the suspension was diluted with water (100 ml) during the acidification. Filtration afforded a solid (4.1 g) which was dried overnight at 50° *in vacuo*. Chromatography on silica of 2.0 g of the material (ethyl acetate to elute) gave 5-amino-*N*-(2,6-diethylphenyl)-3-hydroxy-1*H*-pyrazole-1-carboxamide **11**, (1.1 g, 45%). Also prepared by this method were the pyrazoles **2-5**, **8-12** and **33** in 35, 50, 57, 51, 48, 73, 63, 45, 92 and 100% yield respectively.

5-Amino-*N*-(2,6-diethylphenyl)-3-hydroxy-1*H*-pyrazole-1-carboxamide **11**.

This compound was obtained as a white powder, mp 128-129°; ir (potassium bromide): 3320 (m), 2970 (m), 1689 (s), 1609 (s), 1524 (s), 1497 (s), 1320 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.1 (s, 1), 8.9 (s, 1), 7.1 (m, 3), 6.3 (s, 2), 4.8 (s, 1), 2.5 (q, 4), 1.1 (t, 6).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.43. Found: C, 61.33; H, 6.51; N, 20.14.

5-Amino-4-ethyl-3-hydroxy-1*H*-pyrazole-1-carboxamide **2**.

This compound was obtained as shiny, off white needles, mp 155-157°: ir (potassium bromide): 3492 (m), 3385 (m), 1726 (s), 1643 (m), 1604 (m), 1538 (s), 1420 (s), 749 (m), 767 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 9.8 (s, 1), 6.5-7.3 (bd, 2), 6.2 (s, 2), 2.1 (q, 2), 0.9 (t, 3).

Anal. Cacld. for $C_4H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 41.94; H, 5.64; N, 32.84.

5-Amino-3-hydroxy-4-octyl-1*H*-pyrazole-1-carboxamide **3**.

This compound was obtained as a white solid, mp 118°: ir (potassium bromide): 3100-3400 (broad), 2925 (m), 2852 (m), 1737 (m), 1721 (m), 1589 (s), 1400 (broad) cm^{-1}; ^1H nmr in (DMSO-d_6): δ ppm 9.8 (s, 1), 6.5-7.3 (bd, 2), 6.2 (s, 2), 2.1 (t, 2), 1.2 (s, 12), 0.8 (t, 3).

Anal. Calcd. for $C_{12}H_{22}N_4O_2$: C, 56.67; H, 8.72; N, 22.03. Found: C, 56.46; H, 8.85; N, 21.87.

5-Amino-3-hydroxy-4-phenyl-1*H*-pyrazole-1-carboxamide **4**.

This compound was obtained as shiny, off white solid, mp 162-164°; ir (potassium bromide): 3420 (m), 3320 (m), 3000-3500 (br), 1690 (s), 1600 (s), 1522 (s), 1438 (s), 1253 (s), 705 (m) cm^{-1}; ^1H nmr in (DMSO-d_6): δ ppm 10.7 (s, 1); 6.9-7.5 (m, 5), 6.6 (s, 2).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.95; H, 4.84; N, 25.69.

5-Amino-4-diphenylmethyl-3-hydroxy-1*H*-pyrazole-1-carboxamide **5**.

This compound was obtained as a white solid, mp 134-135°: ir (potassium bromide): 3470 (m), 3000-3500 (br), 1713 (s), 1601 (s), 1522 (m), 1420 (s), 700 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.2 (bs, 1), 7.1-7.3 (m, 10), 6.4-7.2 (bs, 2), 6.3 (s, 2), 5.3 (s, 1).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.30; H, 5.23; N, 18.12.

5-Amino-3-hydroxy-*N*-methyl-1*H*-pyrazole-1-carboxamide **8**.

This compound was obtained as fine white needles, mp 168-169°; ir (potassium bromide): 3430 (m), 3240 (br), 1702 (m), 1718 (m), 1630 (s), 1560 (s), 1347 (m), 997 (m), 763 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 9.9 (bs, 1), 7.4 (q, 1), 6.4 (s, 2), 4.7 (s, 1), 2.7 (d, 3).

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.30; H, 4.99; N, 35.60.

5-Amino-3-hydroxy-*N*-(2-chloroethyl)-1*H*-pyrazole-1-carboxamide **9**.

This compound was obtained as a granular solid, mp 160°; ir (potassium bromide): 3400 (m), 3320 (br), 3200 (br), 1709 (m), 1695 (m), 1620 (s), 1526 (s), 1459 (s) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.0 (s, 1), 7.7 (t, 1), 6.4 (s, 2), 4.7 (s, 1), 3.7 (t, 2), 3.5 (t, 2).

Anal. Calcd. for $C_6H_9ClN_4O_2$: C, 35.22; H, 4.43; N, 27.38. Found: C, 35.10; H, 4.44; N, 27.02.

5-Amino-3-hydroxy-*N*-phenyl-1*H*-pyrazole-1-carboxamide **10**.

This compound was obtained as a white solid, mp 195-196°; ir (potassium bromide): 3420, 3360, 3320 (m), 1705 (s), 1623 (s), 1553 (s), 743 (m): cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.2 (bs, 1), 9.4 (s, 1), 7.6 (d, 2), 7.3 (t, 2), 7.1 (t, 1), 6.5 (s, 2), 4.8 (s, 1).

Anal. Calcd. $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.36; H, 4.86; N, 25.26.

5-Amino-3-hydroxy-*N*-(4-phenoxyphenyl)-1*H*-pyrazole-1-carboxamide **12**.

This compound was obtained as a white solid, mp 179-181°; ir (potassium bromide): 3200-3500 (br), 1712 (m), 1614 (s), 1508 (s), 1490 (s), 1226 (s) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.2 (bs, 1), 9.4 (s, 1), 6.0-7.7 (m, 9), 6.5 (s, 2), 4.8 (s, 1).

Anal. Calcd. for $C_{10}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 61.48; H, 4.42; N, 18.70.

5-Amino-3-hydroxy-4-phenyl-*N*-phenyl-1*H*-pyrazole-1-carboxamide **33**.

This compound was obtained as a white solid, mp 245-246°: ir (potassim bromide) 3430 (m), 3360 (m), 1701 (s), 1605 (s), 1536 (s), 1447 (m), 1362 (m), 754 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.4 (bs, 1), 9.3 (s, 1), 7.0-7.7 (m, 10), 6.7 (s, 2).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.17; H, 4.65; N, 18.94.

General Method For The Thermal Rearrangment Of Pyrazoles **10**, **11** and **12** (Route A).

The pyrazole **11** (0.50 g) was dissolved in ethyl acetate (25 ml) and heated to reflux for 30 minutes. The solution was allowed to cool before hexane was added until the solution became cloudy. The rearranged pyrazole **14** separated out and was dried *in vacuo* at room temperature (0.21 g, 42%).

3-Amino-*N*-(2,6-diethylphenyl)-5-hydroxy-1*H*-pyrazole-1-carboxamide **14**.

This compound was obtained as a white solid, mp 160-161°; ir (potassium bromide): 3100-3500 (br), 1727 (m), 1700 (m), 1640 (s), 1531 (s), 1298 (m), 1240 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.6 (bs, 1), 10.3 (s, 1), 7.0-7.2 (m, 3), 6.5 (s, 2), 4.3 (s, 1), 2.5 (q, 4), 1.1 (t, 6).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.43. Found: C, 61.36; H, 6.64; N, 20.64.

3-Amino-5-hydroxy-*N*-phenyl-1*H*-pyrazole-1-carboxamide **13**.

This compound was obtained as a white solid, mp 207-209°; ir (potassium bromide): 3400 (m), 3200 (br, s), 1700 (s), 1604 (s), 1560 (s), 1219 (s), 751 (s) cm^{-1}; ^1H nmr in (DMSO-d_6): δ ppm 11.1 (bs, 1), 10.6 (bs, 1), 6.9-7.5 (m, 5), 6.5 (s, 2), 4.3 (s, 1).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.12; H, 4.93; N, 25.21.

3-Amino-5-hydroxy-*N*-(4-phenoxyphenyl)-1*H*-pyrazole-1-carboxamide **15**.

This compound was obtained as an off-white solid, mp 194-195°; ir (potassium bromide): 3000-3500 (br), 1699 (s), 1635 (s), 1605 (s), 1563 (s), 1509 (m), 1489 (m), 1212 (s) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 11.1 (s, 1), 10.6 (s, 1), 7.5 (d, 2), 7.4 (t, 2), 7.1 (t, 1), 7.0 (t, 4), 6.7 (s, 2), 4.4 (s, 1).

Anal. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 61.50; H, 4.67; N, 17.72.

3-Amino-5-hydroxy-4-phenyl-*N*-phenyl-1*H*-pyrazole-1-carboxamide **16**.

This compound was obtained as white solid, mp 245-246°; ir (potassium bromide): 3160 (br, s), 1697 (s), 1615 (s), 1566 (s), 1224 (s), 753 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 11.2 (s, 1), 8.7 (bs, 1), 6.9-7.7 (m, 10), 6.7 (bs, 2).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.24; H, 4.99; N, 18.96.

3-Amino-5-hydroxy-1*H*-pyrazole-1-carboxamide **17** (Prepared by Route B).

3-Amino-1*H*-pyrazol-5-ol (5.90 g, 60 mmoles) was dissolved in absolute ethanol (700 ml) and 3,5-dimethyl-1*H*-pyrazole-1-carboxamide (10.5 g, 75 mmoles) was added in one portion and the reaction heated to reflux. After three hours, the reaction was concentrated to a solid, suspended in fresh ethanol (50 ml) then filtered to give a tan powder (7.5 g). Purification was accomplished by dissolving the powder in 2*N* sodium hydroxide solution (20 ml), filtering the insoluble materials then acidification with 2*N* hydrochloric acid (20 ml). The solid obtained was filtered, washed with water then dried *in vacuo* to give **17** (4.25 g, 50%) as a tan solid, mp 180°; ir (potassium bromide): 3400 (s), 1714 (s), 1689 (s), 1650 (s), 1583 (s), 1312 (s), 1371 (s), 632 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ ppm 10.2 (bs, 1), 8.0 (bs, 1), 7.1 (bs, 1), 6.3 (bs, 2), 4.2 (s, 1).

Anal. Calcd. for $C_4H_6N_4O_2$: C, 33.81; H, 4.26; N, 39.42. Found: C, 33.50; H, 4.27; N, 39.60.

REFERENCE AND NOTES

[1] C. N. O'Callaghan, *Proc. R. Ir. Acad. Sect. B.*, **6**, 37 (1976).

[2] In both cases investigated, the reaction of 3-amino-1*H*-pyrazol-5-ol with isocyanates was carried out at room temperature and gave predominantly the 3-amino-5-hydroxy-1*H*-pyrazole-1-carboxamide adducts. No attempt was made to thermally isomerize these product mixtures.

[3] In most cases, these isomeric products were chromatographically more polar and less soluble in organic solvents.

[4] D. Twomey, *J. Org. Chem.*, **31**, 2496 (1966).

[5] The hydrazides described were prepared by a modification of Gagnon and Boivin's procedure [*Can. J. Res.*, **26** Sec. B, 503 (1948)].

They describe quantitative conversion of cyanoesters to hydrazides without solvent. We found that the products crystallized cleanly but in lower yields (unoptimized) from ethanol (Table 1).

[6] Substituted semicarbazides have been prepared by the reaction of isocyanates with hydrazides in refluxing benzene, *e.g.* A. N. Kurtz and C. Niemann, *J. Org. Chem.*, **26**, 1843 (1961). In the cyanoacethydrazide series described in this paper the reactions proceeded smoothly at room temperature in acetonitrile.

[7] In the semicarbazide series, compounds **23-32**, many of the protons in each spectrum appeared as isomeric mixtures in which two proximal absorbances (*ca* 85:15 ratio, major absorbance given first) needed to be taken together to account for the recorded spectrum.

[8] A few examples (**2**, **10**, **12**, **13** and **15**) gave analysis in which one of the measured values was outside the 0.4% limit; all were within 0.48%. No attempt was made to further purify pyrazoles due to their propensity to rearrange upon recrystallization.