Aminopyrazoles. IV (1). Pyrazol-3- and 5-amines from 2,3-Dihaloalkanenitriles or 3-Chloroacrylonitriles and Hydrazines

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2,3-Dihalopropanenitriles and substituted 3-chloropropenenitriles react with hydrazines in basic solution to form either pyrazol-3-amines **4** or pyrazol-5-amines **5** or a mixture of both isomers.

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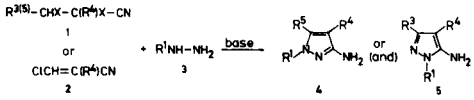
In previous papers (1-3) we reported a facile synthesis of pyrazol-3(5)-amine and 1-alkyl (or aryl)-pyrazol-3-amines from 2-chloroacrylonitrile or 2,3-dichloropropanenitriles and hydrazine or mono-substituted hydrazines in the presence of base.

In this communication we describe the reaction of 2,3-dihaloalkanenitriles **1** or substituted 3-chloropropenenitriles **2** with hydrazine or mono-substituted hydrazines **3** in basic solution leading to the corresponding pyrazol-3(5)-amines and either 1-alkyl(phenyl)-pyrazol-3-amines **4** or 1-alkyl-(phenyl)-pyrazol-5-amines **5** or a mixture of both isomers.

Scheme 1



1	X	$R^{3(5)}$	R^4
a	Cl	CH_3	H
b	Br	C_6H_5	H
c	Br	H	CH_3

3	R^1
k	C_6H_5
m	CH_3
n	$CH_2C_6H_5$
o	$CH(CH_3)_2$
p	C_6H_{11} (cyclohexyl)

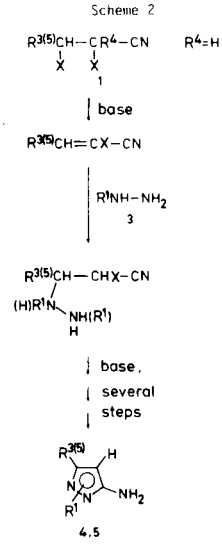
2	R^4
d	H
e	C_6H_5
f	CN

The 2,3-dihaloalkanenitriles **1**, 3-chloropropenenitriles **2** and hydrazines **3**, used in the reaction, are given in Scheme 1 and the reaction products in the Table.

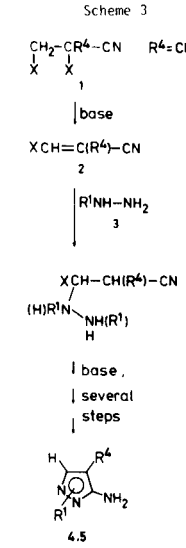
The reaction of 2,3-dichlorobutanenitrile (**1a**) with hydrazines seemed to be quite analogous to that described previously with 2,3-dichloropropanenitrile (2). With hydrazine hydrate (**3k**), phenylhydrazine (**3ℓ**) and methylhydrazine (**3m**) we obtained indeed the expected pyrazol-3-amines (**4ak-m**); with benzylhydrazine (**3n**), however, unexpectedly 1-benzyl-3-methylpyrazol-5-amine (**5an**) is formed.

For the pyrazolaminesynthesis starting from 2,3-dihalopropanenitrile (2) a base induced elimination to 2-haloacrylonitrile as initial step followed by a Michael type addition of the more nucleophilic nitrogen of the hydrazine has been substantiated by Dorn (4). The adaptation of this mechanism to C-substituted 2,3-dihalopropanenitriles is only possible for R^4 = H (Scheme 2).

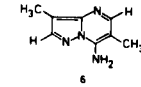
Scheme 2



Scheme 3



In the case of $R^4 \neq H$ (*e.g.*, $R^4 = CH_3$) elimination can only lead to 3-haloalkenenitriles. In order to prove this possibility we used 2,3-dibromo-2-methylpropanenitrile (**1c**) in the reaction with hydrazines **3k-n** (Scheme 3). Hydrazine-hydrate (**3k**) yielded 4-methylpyrazol-3(5)-amine (**4ck**) together with a small amount of 7-amino-3,6-dimethylpyrazolo[1,5-*a*]pyridine (**6**) as a by-product;



methylhydrazine (**3m**) afforded a mixture of 1,4-dimethylpyrazol-3-amine (**4cm**) and 1,4-dimethylpyrazol-5-amine (**5cm**), benzylhydrazine (**3n**) gave 1-benzyl-4-methylpyrazol-5-amine (**5cn**), and **1c** reacted with phenylhydrazine (**3ℓ**) under strong basic conditions to 4-methyl-1-phenylpyrazol-3-amine (**4cℓ**).

Since in the reaction of **1c** with hydrazines in the presence of base the primary step is the formation of

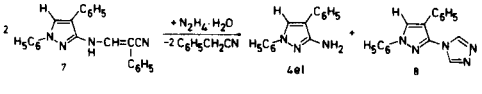
3-halopropenenitrile **2**, to which the hydrazine adds, we examined **2** as reaction component with R^4 = H, C_6H_5, CN, and X = Cl (**2d,e,f**).

A reaction of **2d** with hydrazine has already been observed by Scotti and Frazza (5) yet without success in the isolation of any product. Under variation of the reaction conditions we obtained pyrazol-3(5)-amine (**5dk**) in 48% yield. Further selected examples of pyrazol-3(5)-amine formation from 2- or 3-hetero-substituted 3-haloalkanenitriles were published after conclusion of this work (6).

The pyrazolamines obtained from (*E*)-**2d** with monosubstituted hydrazines are not in all cases the same as those of 2-chloroacrylonitrile (2) (*e.g.*, **5dm**, **5dn** of the Table). In the reaction of 3-chloro-2-phenylpropenenitrile (**2e**) with methylhydrazine (**3m**) in the presence of base the pyrazol-3-amine **4em** is formed while in the cases of the alkylhydrazines **3n-p** a mixture of both isomers **4en-p**, **5en-p**, with the 3-amines **4** as the main products, is obtained. A mixture of **4en-p** and **5en-p** is also obtained when the corresponding hydroxy compound HOCH=C(C_6H_5)CN **2'e** is used in this case with the 5-amino isomer as the main product.

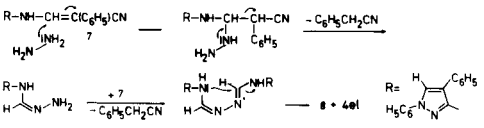
In the reaction of **2e** with phenylhydrazine in the presence of potassium *t*-butoxide in *t*-butyl alcohol the expected and primarily formed 1,4-diphenylpyrazol-3-amine **4e**ℓ was attacked by a further molecule of **2e** with the formation of **7** which could be cleaved by hydrazine-hydrate to **4e**ℓ.

Scheme 4



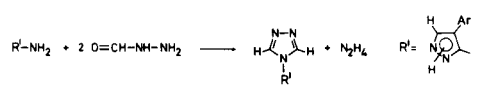
Accompanying products are the 4-(1,4-diphenylpyrazol-3-yl)-4*H*-1,2,4-triazole (**8**) and benzyl cyanide which may be formed by the following reaction sequence:

Scheme 5



A similar incorporation of a formyl group from formylhydrazine into a triazole has been described in the literature (7).

Scheme 6



1-Chloro-2,2-dicyanoethene (**2f**) gave with methylhydrazine in ethanol/sodium ethoxide the pyrazol-3-amine **4fm** while with phenylhydrazine in *t*-butyl alcohol/potassium *t*-butoxide the unexpected pyrazol-5-amine **4f**ℓ is formed (1).

Strucutral Assignments.

The structures of the obtained pyrazolamines, -pyrazol-3- *versus* -5-amines, were confirmed by comparison with samples prepared according to literature methods and with the corresponding isomers (if available) not being identical. The structures of the hitherto unknown pyrazolamines **4e**ℓ, **4en-p**, **5en-p**, unsubstituted in either the 3 or 5-position could be determined by the $\Delta\delta$ (deuteriochloroform-DMSO) method, defined as δ (deuteriochloroform) - δ (DMSO-d_6) and introduced by Elguero and Jacquier (8) ($\Delta\delta$ values see Experimental).

Compound **5f**ℓ whose structure is not unequivocally given in the literature (30 has a $\Delta\delta$ value of -0.21 from which no decision (3- or 5-amino) is possible. It was converted by hydrolysis and decarboxylation to the known 1-phenylpyrazol-5-amine.

EXPERIMENTAL

Melting points were determined on a Bock-monoscope and are uncorrected. The ^{1}H nmr spectra were recorded on Varian A 60, EM 360 or EM 390 spectrometers and the ^{13}C nmr spectra on the HFX 90 multinucleus apparatus from Bruker Instruments using the solvents given in the table with TMS as an internal standard. The ir spectra were obtained on a Beckman IR 4240 in potassium bromide pellets. Analytical data of known compounds, references in the table, are omitted.

Halonitriles.

2,3-Dichlorobutanenitrile (**1a**).

This compound was prepared by pyridine catalyzed chlorine addition to 2-butenenitrile according to Brintzinger (9). After addition of ice water, layer separation was accomplished by addition of methanol to give a colourless liquid, yield 68%, bp 64-68°/13 mm, n_D^{20} = 1.4600 (lit (10) 1.460).

erythro-2,3-Dibromo-3-phenylpropanenitrile (**1b**) (11).

This compound was prepared from cinnamonitrile (12) and bromine in methanol instead of trichloromethane. Colourless crystals with mp 92-93° were obtained in 57% yield; ^{1}H nmr (deuteriochloroform): δ 7.40 (s, 5H, C_6H_5), 5.16 (d, 1H, $^3J_{AB}$ = 9.5 Hz), 4.82 (d, 1H, $^3J_{AB}$ = 9.5 Hz).

2,3-Dibromo-2-methylpropanenitrile (**1c**) (13), 3-Chloropropenenitrile (**2d**) (14), 3-Chloro-2-phenylpropenenitrile (**2e**) (15), and 1-Chloro-2,2-dicyanoethene (**2f**) (16).

Compounds **1c**, **2d**, **2e** and **2f** were prepared by known methods.

Hydrazines.

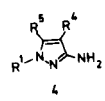
Hydrazine-hydrate and methylhydrazine are commercially available; benzylhydrazine (17), isopropylhydrazine (18) and cyclohexylhydrazine (19) were prepared according to literature methods.

Method A (Potassium Carbonate in Water as Solvent).

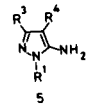
2,3-Dihaloalkanenitrile (0.2 mole) was added dropwise to a well stirred and cooled (0-5°) solution of 57 g (0.41 mole) of potassium carbonate and 0.22 mole of hydrazine or alkylhydrazine respectively, in 80 ml of water. The reaction mixture was then stirred at room temperature for 5 hours and for an additional 24 hours at 50-60°. The pyrazolamine was extracted with ether using a rotary perforator. The extraction time depends

Table

Preparation of Pyrazol-3-amines **4** and (or) -5-amines **5**



4



5

4,5	R^1	R^4	R^5 in **4** or R^3 in **5**	Method	Yield %	Mp (°C) (bp/mm Hg)	^{1}H NMR (deuteriochloroform) δ (TMS)	Ref
4ak	H	H	CH_3	A A′	64 65.5	(130/0.6) 211 (a)	6.3 (s, broad, 3H, NH, NH_2, exchangeable), 5.28 (q, 1H, 4-H, J = 0.6 Hz), 2.06 (d, 3H, 3(5)-CH_3, J = 0.6 Hz)	(24)
4al	C_6H_5	H	CH_3	B	11.5	88-89 160 (a)	7.42 (s, 5H, C_6H_5), 5.63 (s, 1H, 4-H), 3.7 (s, broad, 2H, NH_2, exchangeable), 2.30 (s, 3H, 5-CH_3)	(25)
4am	CH_3	H	CH_3	A	84	65.5-68 (98/3) 207-208 (a)	5.38 (s, 1H, 4-H), 3.58 (s, N-CH_3), overlayed by 3.55 (s, broad, NH_2, together 5H), 2.15 (s, 3H, 5-CH_3)	(27)
5an	$CH_2C_6H_5$	H	CH_3	A	49	67-70.5 139-142 (a)	7.0-7.5 (m, 5H, C_6H_5), 5.36 (s, 1H, 4-H), 5.12 (s, 2H, -CH_2-), 3.3 (s, broad, 2H, NH_2), 2.18 (s, 3H, 3-CH_3)	(22)
4bk	H	H	C_6H_5	A′	91	127 202 (a)	7.2-7.7 (m, 5H, -C_6H_5), 5.9 (s, 4H, NH, NH_2, 4-H, 3H, exchangeable)	(31)
4bm	CH_3	H	C_6H_5	C	39	94-95 175-179 (a)	7.38 (s, 5H, C_6H_5), 5.66 (s, 1H, 4-H), 3.68 (s, 3H, N-CH_3), 3.39 (s, 2H, NH_2, exchangeable)	(28)
4ck	H	CH_3	H	D	25	(121-124/0.4) 219-221 (a)	7.08 (s, 1H, 4-H), 6.5 (s, broad, 3H, NH, NH_2), 1.83 (s, 3H, 4-CH_3)	(21)
4cl	C_6H_5	CH_3	H	B	35	127-129 210-211 (a)	7.00-7.67 (m, 6H, C_6H_5, 5-H), 3.70 (s, broad, 2H, NH_2, exchangeable), 1.98 (s, 3H, 4-CH_3)	(25)
4cm	CH_3	CH_3	H	D	10	(64-75/0.3) 204-206 (a)	6.83 (s, 1H, 5-H), 4.22 (s, broad, 2H, NH_2, exchangeable), 3.47 (s, 3H, N-CH_3), 1.77 (s, 3H, 4-CH_3)	(21)
5cm	CH_3	CH_3	H	D	30	135-136 245 (a)	7.11 (s, 1H, 3-H), 3.67 (s, 3H, N-CH_3), 3.25 (s, broad, 2H, NH_2, exchangeable), 1.92 (s, 3H, 4-CH_3)	(21,22)
5cn	$CH_2C_6H_5$	CH_3	H	D	28	129-131 159-160 (a)	6.96 (s, 1H, 3-H), overlayed by 6.8-7.5 (m, 5H, C_6H_5), 5.10 (s, 2H, N-CH_2-), 4.84 (s, broad, 2H, NH_2, exchangeable), 1.83 (s, 3H, 4-CH_3)	(22)
4dk	H	H	H	C	60	(110/0.1) 216 (a)	7.33 (d, 1H, 5(3)-H, J = 2 Hz), 5.67 (d, 1H, 4-H, J = 2 Hz), 4.5 (s, broad, 3H, NH, NH_2)	(2,3)
5dm	CH_3	H	H	C	50	71-72	7.73 (d, 1H, 3-H, J = 2 Hz), 5.48 (d, 1H, 4-H, J = 2 Hz), 3.75 (s, broad, 2H, NH_2, exchangeable), 3.62 (s, 3H, N-CH_3)	(29)
5dn	$CH_2C_6H_5$	H	H	C	49	79	6.98-7.49 (m, C_6H_5), overlayed by 7.29 (d, 3-H, J = 2 Hz), together 6H, 5.57 (d, 1H, 4-H, J = 2 Hz), 5.22 (s, 2H, N-CH_2-C_6H_5), 3.4 (s, broad, 2H, NH_2)	(22)

Table, continued

Preparation of Pyrazol-3-amines **4** and (or) -5-amines **5**

4,5	R^1	R^4	R^5 in **4** or R^3 in **5**	Method	Yield %	Mp (°C) (bp/mm Hg)	^{1}H NMR (deuteriochloroform) δ (TMS)	Ref
4ek	H	C_6H_5	H	E	63	176	(DMSO-d_6): 7.70 (s, 3(5)-H), overlayed by 7.0-7.9 (m, C_6H_5), together 6H, 6.6 (s, broad, 3H, NH, NH_2)	(23)
4el	C_6H_5	C_6H_5	H	B (in the first step)	37 (overall yield)	68 163-164 (a)	7.81 (s, 1H, 5-H), 7.00-7.73 (m, 10H, 1-C_6H_5, 4-C_6H_5), 3.97 (s, 2H, NH_2, exchangeable)	
4em	CH_3	C_6H_5	H	E	84	119 215 (a)	7.06-7.57 (m, 6H, 4-C_6H_5, 5-H), 3.75 (s, 3H, N-CH_3), 3.53 (s, broad, 2H,NH_2, exchangeable)	(28)
4en	$CH_2C_6H_5$	C_6H_5	H	E	49	112 173 (a)	7.0-7.6 (m, 11H, 5-H, 4-C_6H_5, N-CH_2-C_6H_5), 5.10 (s, 2H, N-CH_2-C_6H_5), 3.80 (s, broad, 2H, NH_2, exchangeable)	
4eo	$(CH_3)_2CH$	C_6H_5	H	E	42	73 196-198 (a)	7.45 (s, 5-H) together with 7.12-7.58 (m, 4-C_6H_5, 6H), 4.28 (sept. 1H, N-$CH(CH_3)_2$, J = 7 Hz), 3.8 (s, broad, NH_2, exchangeable), 1.47 (d, 6H, N-$CH(CH_3)_2$, J = 7 Hz)	
5eo	$(CH_3)_2CH$	C_6H_5	H	E	10	79 139-141 (a)	7.55 (s, 1H, 3-H), 7.13-7.52 (m, 5H, 4-C_6H_5), 4.42 (sept. 1H, N-$CH(CH_3)_2$, J = 7 Hz), 3.7 (s, broad, NH_2, exchangeable), 1.53 (d, 6H, N-$CH(CH_3)_2$, J = 7 Hz)	
4ep	C_6H_{11}	C_6H_5	H	E	30	100 180 (a)	7.0-7.6 (m, 4-C_6H_5, 5-H), 3.82 (m, broad, 3H, N-CH<, NH_2, 2H, exchangeable), 0.9-2.5 (m, broad, 10H, cyclohexyl)	
5ep	C_6H_{11}	C_6H_5	H	E	13	123-124 205 (a)	7.53 (s, 3-H) together with 7.13-7.67 (m, 4-C_6H_5, 6H), 3.5-4.2 (m, 3H, N-CH<, NH_2, 2H, exchangeable), 1.0-2.3 (m, 10H, cyclohexyl)	
5f[l]	C_6H_5	CN	H	B	12	137	7.51 (s, 1H, 3-H), 7.47 (s, 5H, N-C_6H_5), 4.72 (s, broad, 2H, NH_2, exchangeable)	(30)
4fm	CH_3	CN	H	E	66	126	7.47 (s, 1H, 5-H), 4.2 (s, broad, 2H, NH_2), 3.73 (s, 3H, N-CH_3)	(20b)

(a) Mp of picrate.

on the solubility of the pyrazolamine in water. After evaporation of the ether the residue was purified by distillation or column chromatography.

3(5)-Methylpyrazol-5(3)-amine (**4ak**).

This compound was prepared from 11 g (0.22 mole) of **3k** hydrate and 27.6 g (0.2 mole) of **1a**. The extraction time was 48 hours and the yield of **4ak** amounted to 12.4 g (64%), bp 130°/0.6 mm; ^{1}H nmr: see Table.

1,5-Dimethylpyrazol-3-amine (**4am**).

This compound was obtained from 10.1 g (0.22 mole) of **3m** and 27.6 g (0.2 mole) of **1a**. The yield of **4am** amounted to 18.7 g (84%), bp 98°/3 mm, mp 65.5-68° (from benzene/petroleum ether 50/50, v/v); ir (potassium bromide): 3390, 3310, 1560, 1485, 745 cm^{-1}; ^{1}H nmr: see Table.

1-Benzyl-3-methylpyrazol-5-amine (**5an**).

This compound was obtained from 27.0 g (0.22 mole) of **3n** and 27.6 g (0.2 mole) of **1a**. The extraction time was 16 hours. From the crude oily product (30.9 g) an aliquot of 2.7 g was chromatographed on 150 g of silica gel with acid free ethyl acetate, yield 1.6 g (49%) of **5an**; mp 67-70.5° (after sublimation at 60-100°/0.05 mm); ir (potassium bromide): 3450, 3370, 3220, 2960, 2930, 1620, 1560, 1500, 1460, 1390 cm^{-1}; ^{1}H nmr: see Table.

Method A'. Procedure as Described in Method A, But With Admixture of Methanol as Dissolution Promoter.

3(5)-Methyl-5(3)-amine (**4ak**).

Compound **1a** (27.6 g, 0.2 mole) was added dropwise at 5-10° to a well stirred mixture of 11 g (0.22 mole) of **3k** hydrate and 57 g (0.41 mole) of potassium carbonate in 150 ml of methanol and 50 ml of water. The work up procedure was the same as described in method A. The yield of crude **4ak** was 18.5 g (93%) and after distillation 12.7 g (65.5%), bp 130°/0.6 mm.

3(5)-Phenylpyrazol-5(3)-amine (**4bk**).

This compound was prepared from 29 g (0.2 mole) of potassium carbonate in 40 ml of water, 6 g (0.12 mole) of **3k** hydrate and 29 g (0.1 mole) of **1b** in 150 ml of methanol. The extraction time was 24 hours and the yield of **4bk** was 14.5 g (91%), mp 127° (from benzene).

Method B (Potassium *t*-Butoxide in *t*-Butyl Alcohol).

Potassium was dissolved in *t*-butyl alcohol under reflux, **31** was added to the hot solution and after cooling to 5°, **1a**, **1c** or **2** was added dropwise with vigorous stirring. Then the mixture was refluxed for 3 hours. After addition of water the solvent was evaporated under reduced pressure and the resulting residue was reslurrished in water and extracted continuously with ether.

5-Methyl-1-phenylpyrazol-3-amine (**4a***ℓ*).

This compound was obtained from 20 g (0.5 mole) of potassium in 500 ml of *t*-butyl alcohol, 21.6 g (0.2 mole) of **31** and 27.6 g (0.2 mole) of **1a**. The product separated from a concentrated and chilled ethereal solution, yield 4.0 g (11.5%), mp 88-89° (from water by decolorization with charcoal); ir (potassium bromide): 3415, 3305, 3205, 1605, 1595, 1510, 1500, 1395, 795, 765, 700, 675 cm^{-1}; ^1H nmr: see Table.

4-Methyl-1-phenylpyrazol-3-amine (**4c***ℓ*).

This compound was obtained from 13 g (0.33 mole) of potassium in 250 ml of *t*-butyl alcohol, 21.6 g (0.2 mole) of **3***ℓ* and 45.4 g (0.2 mole) of **1c**. The residue from the ether extract was treated with boiling cyclohexane from which **4c***ℓ* separated after cooling, yield 12.1 g (35%), mp 127-129° (from water with decolorizing carbon); ir (potassium bromide): 3415, 3305, 3205, 1640, 1600, 1585, 1505, 1405, 935, 680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.84 (q, 1H, 5-H, J = 0.9 Hz), 6.83-7.75 (m, 5H, C_6H_5), 4.9 (s, broad, 2H, NH_2, exchangeable), 1.95 (d, 3H, 4-CH_3, J = 0.9 Hz); Δδ (deuteriochloroform-DMSO): (5-H) = −0.17 from which follows the 3-amino structure.

1,4-Diphenylpyrazol-3-amine (**4e***ℓ*).

(a) 2-Phenyl-2-[(1,4-diphenylpyrazol-3-yl)amino]propenenitrile (**7**) was prepared from 8 g (0.2 mole) of potassium in 300 ml of *t*-butyl alcohol, 10.8 g (0.1 mole) of **2e** in 100 ml of *t*-butyl alcohol and 50 ml of tetrahydrofuran, yield 8.2 g (45%) of **7**, pale yellow crystals, mp 182° (from 1-propanol); ir (potassium bromide): 2200 (C≡N), 1635, 1600, 1590, 1525, 1510, 1410, 1365, 1295, 1265, 765, 755, 690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.31 (d, 1H, ^3J = 13 Hz, s after addition of deuterium oxide), 7.07-7.87 (m, 15H, 2-C_6H_5, 1-C_6H_5, 4-C_6H_5), 6.5 (s, broad, 1H, disappears after addition of deuterium oxide; ^1H nmr (DMSO-d_6): δ 9.67 (d, broad, 1H, ^3J = 11 Hz, NH), 8.82 (s, 1H, 5-H), 6.8-8.2 (m, 16H, 3-H, 1-C_6H_5, 2-C_6H_5, 4-C_6H_5); Δδ (deuteriochloroform-DMSO): (5-H) = −0.87 ppm; from this value follows the pyrazol-3-amine partial structure; ^{13}C nmr (DMSO-d_6): δ 147.48 (q), 143.97 (CH), 139.06 (q), 133.88 (q), 131.19 (q), 129.41, 128.87, 128.71, 127.41, 127.03, 126.66, 125.90, 125.68, 123.36, 117.70, 114.52 (CH + q), 83.34 (q) (q = quarternary carbon).

Anal. Calcd. for $C_{24}H_{18}N_4$ (362.44): C, 79.54; H, 5.01; N, 15.46. Found: C, 79.23; H, 5.03; N, 15.38.

(b) Hydrazinolysis of **7**. Compound **7** (7.25 g, 20 mmoles) and 10 g (0.2 mole) of **3k** hydrate were refluxed in 100 ml of ethanol for 6 hours. After removal of the solvent *in vacuo* and addition of a small amount of ether, crystals of 4-(1,4-diphenylpyrazol-3-yl)-4*H*-1,2,4-triazole (**8**) were collected by suction, yield 1.5 g (52%), mp 200° (from ethanol); ir (potassium bromide): 1540, 765, 755 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.46 (s, 2H, 3-H, 5-H of triazole), 8.12 (s, 1H, 5-H of pyrazole), 7.17-7.97 (m, 10H, 1-C_6H_5, 4-C_6H_5); ^1H nmr (DMSO-d_6): δ 9.17 (s, 1H, 5-H of pyrazole), 8.98 (s, 2H, 3-H, 5-H of triazole), 7.13-8.37 (m, 10H, 1-C_6H_5, 4-C_6H_5); ^{13}C nmr (deuteriochloroform): δ 141.65 (CH), 141.11 (q), 139.28 (q), 130.00 (CH), 129.62 (CH), 129.24 (q), 128.71, 128.22 (CH), 127.90 (CH), 127.46, 119.32 (CH), 117.54 (q).

Anal. Calcd. for $C_{17}H_{13}N_5$ (287.33): C, 71.07; H, 4.56; N, 24.37. Found: C, 70.80; H, 4.84; N, 24.12.

The filtrate was chromatographed on 200 g of silica gel with ether as the eluent yielding 3.2 g of a reddish oil which was distilled under reduced pressure to give 1.0 g of a fraction with bp 30-51°/0.05 mm, identified as benzyl cyanide (41%) and 1.9 g (82%) of **4e***ℓ*, bp 195°/0.05 mm, which solidified, mp 68°; ir (potassium bromide): 3420, 3270, 3180, 1610, 1600, 1585, 1515, 1480, 1420, 755, 690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.55 (s, 1H, 5-H), 7.03-7.92 (m, 10H, 1-C_6H_5, 4-C_6H_5), 5.07 (s, 2H, NH_2); Δδ (deuteriochloroform-DMSO): (5-H) = −0.74 ppm from which follows the 3-amino structure.

Anal. Calcd. for $C_{15}H_{13}N_3$ (235.29): C, 76.57; H, 5.57; N, 17.86. Found: C, 76.30; H, 5.70; N, 17.86.

5-Amino-1-phenylpyrazole-4-carbonitrile (**5f***ℓ*).

This compound was obtained from 8 g (0.2 mole) of potassium, 10.8 g (0.1 mole) of **3***ℓ* and 11.25 g (0.1 mole) of **2f** (16), yield 2.2 g (12%) of **5f***ℓ*, mp 137° (from water with a small amount of decolorizing carbon), mp lit (30) 140°; identical ir spectra; ^1H nmr (DMSO-d_6): δ 7.78 (s, 1H, 3-H), 7.51 (s, 5H, N-C_6H_5), 6.62 (s, broad, 2H, NH_2); Δδ (deuteriochloroform-DMSO): (3-H) = −0.21 ppm.

1-Phenylpyrazole-5-amine.

One g (5.4 mmoles) of **5f***ℓ* was refluxed in 25 ml of 2*N* sodium hydroxide for 6½ hours. After filtration the solution was adjusted to *p*H ~5 with about 25 ml of 2*N* hydrochloric acid giving 0.97 g (88%) of 5-amino-1-phenylpyrazole-4-carboxylic acid, mp 190-192° (with decarboxylation) (lit (20) mp 173-174°), 0.95 g (4.7 mmoles) of this carboxylic acid was heated at 250° until the carbon dioxide evolution came to an end, yield 0.63 g (85%) of 1-phenylpyrazol-5-amine with mp 40° (lit (20) mp 50-51°); ^1H nmr (deuteriochloroform): δ 7.17-7.73 (m, 6H, 3-H, 1-C_6H_5), 5.56 (d, 1H, ^3J = 1.8 Hz, 4-H), 3.82 (s, broad, 2H, NH_2).

Method C (With Excess of Hydrazine as Proton Acceptor).

To a mixture of the hydrazine and methanol the halo compound (solid or methanolic solution) was added in small portions. After completion of the reaction the solvent was removed *in vacuo* and after addition of water the residue was extracted continuously with ether.

1-Methyl-5-phenylpyrazol-3-amine (**4bm**).

This compound was obtained from 13.8 g (0.3 mole) of **3m** in 150 ml of methanol and 28.9 g (0.2 mole) of **1b**. The mixture was allowed to stand at room temperature for 14 days, yield 14.9 g (86%) of crude **4bm**, after chromatography of 2 g on 200 g of silica gel with ether the yield diminished to 0.9 g (39%) of **4bm**, mp 94-95° (from ether); ir (potassium bromide): 3390, 3310, 3220, 1550, 745, 695 cm^{-1}; ^1H nmr: see Table.

Anal. Calcd. for $C_{10}H_{11}N_3$ (173.22): C, 69.34; H, 6.40; N, 24.26. Found: C, 69.06; H, 6.61; N, 24.20.

Pyrazol-3(5)-amine (**4dk**).

This compound was obtained from 11 g (0.22 mole) of **3k** hydrate in 50 ml of methanol and 8.75 g (0.1 mole) of **2d**. After 4 hours reflux the aqueous layer was saturated with sodium chloride and the yield after extraction was 5 g (60%), bp 110°/0.1 mm; ^1H nmr: see Table.

1-Methylpyrazol-5-amine (**5dm**).

This compound was obtained from 9.2 g (0.2 mole) of **3m** in 50 ml of methanol and 8.75 g (0.1 mole) of **2d**. After 5 hours reflux, the aqueous layer was made alkaline with 2*N* sodium hydroxide before extraction, yield 4.9 g (50%) of **5dm** after distillation, bp 98-105°/0.5 mm, mp 71-72° from diisopropyl ether; ir (potassium bromide): 3410, 3325, 3165, 1565, 1435 cm^{-1}; ^1H nmr: see Table.

1-Benzylpyrazol-5-amine (**5dn**).

This compound was prepared from 24.4 g (0.2 mole) of freshly distilled **3n** (17) in 50 ml of methanol and 8.75 g (0.1 mole) of **2d**. After 8 hours reflux 12.2 g (82%) of crude **5dn** were obtained, 3 g of which were chromatographed on 200 g of silica gel with ether/ethyl acetate 1/1, v/v. The yield then diminished to 1.8 g (49%) of **5dn**, mp 79° (from petroleum ether 60-70°), ir (potassium bromide): 3340, 3300, 3160, 1635, 1560, 1510, 1495, 1455, 1420, 1240, 925, 760, 735, 700 cm^{-1}; ^1H nmr (deuteriochloroform): see Table; ^1H nmr (DMSO-d_6): δ 6.98-7.43 (m, C_6H_5) overlayed by 7.08 (d, ^3J = 1.76 Hz, 3-H) together 6H, 5.30 (d, 1H, ^3J = 1.76 Hz) overlayed by a broad signal at 5.27 (s, NH_2) and 5.13 (s, N-CH_2-C_6H_5) together 5H; Δδ (deuteriochloroform-DMSO): (3-H) = +0.21 ppm from which follows the 5-amino structure.

Method D (Potassium Hydroxide in Methanol).

To a solution of powdered potassium hydroxide in methanol was added the hydrazine and then the dibromoalkanenitrile while cooling with ice. The reaction mixture was stirred overnight at room temperature and was then refluxed for 5 hours. After evaporation of the solvent *in vacuo* water was added before extraction with ether.

4-Methylpyrazol-3(5)-amine (**4ck**).

This compound was obtained from 70.0 g (1.2 mole) of potassium hydroxide in 500 ml of methanol, 70.1 g (1.4 mole) of **3k** hydrate and 136.1 g (0.6 mole) of **1c**, yield 14.5 g (25%) of **4ck** with bp 121-124°/0.4 mm; ^{1}H nmr: see Table.

7-Amino-3,6-dimethylpyrazolo[1,5-a]pyrimidine (**6**) (21).

From this oil 200 mg (0.4%) of **6** separated, mp 235° from ethanol, sublimable at 100-130°/0.4 mm; ir (potassium bromide): 3320, 3160, 1650, 1615, 1550 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.97 (s, 1H, 2-H or 5-H), 7.85 (s, 5-H or 2-H), 7.33 (s, broad, 2H, NH_2), 2.23 (s, 3H, 3-CH_3 or 6-CH_3), 2.18 (s, 3H, 6-CH_3 or 3-CH_3); ^{13}C nmr (DMSO-d_6): δ 149.36 (CH), 145.97 (q), 145.64 (q), 142.57 (CH), 101.57 (q), 94.07 (q), 12.08 (CH_3), 7.44 (CH_3).

1,4-Dimethylpyrazol-3-amine (**4cm**) and 1,4-Dimethylpyrazol-5-amine (**5cm**).

These two compounds were obtained from 70.0 g (1.2 mole) of potassium hydroxide in 600 ml of methanol, 27.6 g (0.6 mole) of **3m** and 136.2 g (0.6 mole) of **1c** (21,22). From the ether extract 20 g (30%) of **5cm** separated, mp 135-136° (after sublimation at 80°/0.05 mm); ir (potassium bromide): 3380, 3300, 3135, 1640, 1585, 1535, 1430, 1410, 970 cm^{-1}; ^{1}H nmr (DMSO-d_6): 6.88 (s, 1H, 3-H), 4.74 (s, broad, 2H, NH_2, exchangeable), 3.48 (s, 3H, N-CH_3), 1.79 (s, 3H, 4-CH_3); Δδ (deuteriochloroform-DMSO): (3-H) = +0.22 ppm from which follows the 5-amino structure. The ethereal mother liquor was evaporated and the residue distilled, giving 6.6 g (10%) of **4cm** as a pale yellow oil with bp 64-75°/0.3 mm; ir (potassium bromide): 3340, 3220, 3110, 2940, 1655, 1620, 1590, 1510, 1465, 1420, 1200, 1180, 1155, 810 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.00 (s, 1H, 5-H), 3.85 (s, broad, 2H, NH_2, exchangeable), 3.50 (s, 3H, N-CH_3), 1.80 (s, 3H, 4-CH_3); Δδ (deuteriochloroform-DMSO): (5-H) = −0.17 ppm from which follows the 3-amino structure.

1-Benzyl-4-methylpyrazol-5-amine (**5cn**).

This compound was obtained from 34.2 g (0.6 mole) of potassium hydroxide in 400 ml of methanol, 36.7 g (0.3 mole) of **3n** and 68.1 g (0.3 mole) of **1c**, yield 15.9 (28%) of **5cn** (22) with bp 136-153°/0.5 mm, mp 129-131° (from benzene/petroleum ether 1/1, v/v); ir (potassium bromide): 3430, 3290, 3150, 1640, 1530, 1415, 730 cm^{-1}; ^{1}H nmr: see Table.

Method E (Sodium Ethoxide in Ethanol).

To a solution of the 3-chloropropenenitrile in ethanol an equivalent amount of the hydrazine in ethanol was given and then sodium ethoxide (prepared *in situ* by addition of sodium hydride). After stirring for 10 hours the ethanol was evaporated under reduced pressure and the residue was taken up in water and extracted continuously with ether.

4-Phenylpyrazol-3-(5)-amine (**4ek**).

This compound was obtained from 8.18 g (50 mmoles) of **2e** (*Z*-isomer) (14) in 50 ml of ethanol, 2.5 g (50 mmoles) of **3k** hydrate in 50 ml of ethanol and 1.3 g (54 mmoles) of sodium hydride, yield 5.1 g (63%) of **4ek** with mp 176° (from ethanol); ^{1}H nmr: see Table.

1-Methyl-4-phenylpyrazol-3-amine (**4em**).

This compound was obtained from 8.18 g (50 mmoles) of **2e** (*E*- or *Z*-isomer) (14) in 50 ml of ethanol, 2.3 g (50 mmoles) of **3m** in 50 ml of ethanol and 1.0 g (54 mmoles) of sodium hydride, yield 7.3 g (84%) of crude **4em**, mp 119° (from diisopropyl ether); ir (potassium bromide): 3450, 3360, 1515, 1490, 1445, 1180, 775 cm^{-1}.

1-Benzyl-4-phenylpyrazol-3-amine (**4en**).

This compound was prepared from 8.2 g (50 mmoles) of **2e** (*E*- or *Z*-isomer) (14) in 50 ml of ethanol, 6.1 g (50 mmoles) of **3n** (16) in 50 ml of ethanol and 1.3 g (54 mmoles) of sodium hydride, yield 6.0 g (49%) of **4en** with mp 113° (from diisopropyl ether); ir (potassium bromide): 3430, 3290, 3190, 1610, 1570, 1520, 1410, 760, 695 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.83 (s, 1H, 5-H), 6.97-7.63 (m, 10H, 4-C_6H_5, N-CH_2-C_6H_5), 5.07 (s, 2H, N-CH_2-C_6H_5), 4.63 (s, broad, 2H, NH_2); Δ δ (deuteriochloroform-DMSO): (5-H) = −0.23 ppm from which follows the 3-amino structure.

Anal. Calcd. for $C_{16}H_{15}N_3$ (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.10; H, 6.30; N, 16.94.

1-Benzyl-4-phenylpyrazol-5-amine (**5en**).

This compound was prepared for comparison from 7.25 g (50 mmoles) of 3-hydroxy-2-phenylpropenenitrile (23) and 6.1 g (50 mmoles) of **3n** in 150 ml of ethanol under reflux for 20 hours, yield 11.4 g (91.5%) of **5en** with mp 126-127° (from diisopropyl ether); ir (potassium bromide): 3460, 3440, 3310, 3160, 1610, 1580, 1530, 760, 695, cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.57 (s, 1H, 5-H), 7.10-7.55 (m, 10H, 4-C_6H_5, N-CH_2-C_6H_5), 5.25 (s, 2H, N-CH_2-C_6H_5), 3.63 (s, broad, NH_2, exchangeable); ^{1}H nmr (DMSO-d_6): δ 7.55 (s, 5-H) integrated with 7.1-7.73 (m, 4-C_6H_5, N-CH_2-C_6H_5) together 11H, 5.47 (s, broad, 2H, NH_2, exchangeable), 5.27 (s, 2H, N-CH_2-C_6H_5); Δ δ (deuteriochloroform-DMSO): (5-H) = +0.02 ppm from which follows the 5-amino structure.

Anal. Calcd. for $C_{16}H_{15}N_3$ (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.22; H, 6.20; N, 16.90.

1-Isopropyl-4-phenylpyrazol-3-amine (**4eo**) and 1-Isopropyl-4-phenylpyrazol-5-amine (**5eo**).

These two compounds were prepared from 8.2 g (50 mmoles) of **2e** (*E*-or *Z*-isomer) (14) in 50 ml of ethanol, 3.7 g (50 mmoles) of **3o** (17) in 50 ml of ethanol and 1.3 g (54 mmoles) of sodium hydride, yield 10.1 g of an oily product of which 5 g were chromatographed on 150 g of silica gel with ether as eluent; yield 0.5 g (10%) of **5eo** with mp 79° (from petroleum ether 60-70°) and Rf 0.35 (silica gel, ether); ir (potassium bromide): 3440, 3310, 3220, 1635, 1610, 1585, 1575, 1520, 1445, 1410, 1370, 1220, 950, 765, 700 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.47 (s, 3-H) together with 7.0-7.6 (m, 4-C_6H_5) 6H, 5.27 (s, broad, 2H, NH_2), 4.58 (sept, 1H, N-CH(CH_3)$_2$, J = 7 Hz), 1.33 (d, 6H, N-CH(CH_3)$_2$, J = 7 Hz); Δ δ (deuteriochloroform-DMSO): (3-H) = +0.08 ppm from which follows the 5-amino structure.

Anal. Calcd. for $C_{12}H_{15}N_3$ (201.27): C, 71.61; H, 7.51; N, 20.88. Found: C, 71.84; H, 7.76; N, 20.86.

There was also obtained 2.1 g (42%) of **4eo** with mp 73° (from petroleum ether 60-70°) and Rf 0.2 (silica gel, ether); ir (potassium bromide): 3400, 3180, 1630, 1610, 1585, 1510, 1455, 765, 695 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.77 (s, 1H, 5-H), 7.0-7.65 (m, 5H, 4-C_6H_5), 4.58 (s, 2H, NH_2), 4.25 (sept., 1H, N-CH(CH_3)$_2$, J = 7 Hz), 1.37 (d, 6H, N-CH(CH_3)$_2$, J = 7 Hz); Δ δ (deuteriochloroform-DMSO): (5-H) = -0.32 ppm from which follows the 3-amino structure.

Anal. Calcd. for $C_{12}H_{15}N_3$ (201.27): C, 71.61; H, 7.51; N, 20.88. Found: C, 71.79; H, 7.78; N, 20.65.

1-Cyclohexyl-4-phenylpyrazol-3-amine (**4ep**) and 1-Cyclohexyl-4-phenylpyrazol-5-amine (**5ep**).

These two compounds were obtained from 8.2 g (50 mmoles) of **2e** (*E*-or *Z*-isomer) (14), 7.5 g (50 mmoles) of **3p** (18) and 1.3 g (54 mmoles) of sodium hydride, yield 11.6 g of a semicrystalline product of which 5.6 g were chromatographed on silica gel with ether as eluent, yield 3.6 g (30%) of **4ep** with mp 100° (from diisopropyl ether) and Rf 0.25 (silica gel, ether); ir (potassium bromide): 3430, 3290, 3190, 2940, 1610, 1510, 1450, 755, 690 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.75 (s, 1H, 5-H), 6.85-7.72 (m, 5H, 4-C_6H_5), 4.62 (s, broad, 2H, NH_2), 3.57-4.22 (m, 1H, N-CH<), 0.8-2.4 (m, 10H, cyclohexyl); Δ δ (deuteriochloroform-DMSO): (5-H) = -0.15 ppm from which follows the 3-amino structure.

Anal. Calcd. for $C_{15}H_{19}N_3$ (241.34): C, 74.65; H, 7.94; N, 17.41. Found: C, 74.30; H, 7.97; N, 17.69.

There was also obtained 1.6 g (13%) of **5ep** with mp 123-124° (from diisopropyl ether) and Rf 0.7 (silica gel, ether); ir (potassium bromide): 3440, 3400, 3310, 2950, 2860, 1640, 1610, 1575, 1535, 1510, 1450, 1420,

955, 945, 765, 700 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.45 (s, 3-H) overlayed by 7.00-7.67 (m, 4-C_6H_5) together 6H, 5.27 (s, 2H, NH_2), 3.87-4.47 (m, 1H, N-CH<), 0.93-2.10 (m, 10H, cyclohexyl); Δ δ (deuteriochloroform-DMSO): (3-H) = +0.08 ppm from which follows the 5-amino structure.

Anal. Calcd. for $C_{15}H_{19}N_3$ (241.34): C, 74.65; H, 7.94; N, 17.41. Found: C, 74.54; H, 7.97; N, 17.61.

3-Amino-1-methylpyrazol-4-carbonitrile (**4fm**).

This compound was obtained from 2.3 g (50 mmoles) of **3m**, 5.63 g (50 mmoles) of **2f** (19) and 1.3 g (54 mmoles) of sodium hydride, yield 4.0 g (66%) of **4fm** with mp 126° (from ethanol); ir (potassium bromide): 3440, 3350, 3250, 2215 (C≡N), 1650, 1575, 1525, 1110 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.00 (s, 1H, 5-H), 5.5 (s, broad, 2H, NH_2, exchangeable), 3.65 (s, 3H, N-CH_3); Δ δ (deuteriochloroform-DMSO): (5-H) = -0.53 ppm from which follows the 3-amino structure.

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REFERENCES AND NOTES

(1) G. Ege and H. Franz, *J. Heterocyclic Chem.*, **19**, 1265 (1982).

(2) G. Ege and P. Arnold, *Synthesis*, 52 (1976).

(3) G. Ege and P. Arnold, *Angew. Chem.*, **86**, 237 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 206 (1974).

(4) H. Dorn and R. Ozegowski, *J. Prakt. Chem.*, **321**, 93 (1979).

(5) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

(6) F. Pochat, *Tetrahedron Letters*, 2991 (1979); K. Issleib and H. Schmidt, *Z. Anorg. Allg. Chem.*, **459**, 131 (1979).

(7) S. A. Lang Jr., F. M. Lovell and E. Cohen, *J. Heterocyclic Chem.*, **14**, 65 (1977).

(8) J. Elguero and R. Jacquier, *J. Chim. Phys.*, **63**, 1242 (1966); J. Elguero, R. Jacquier and S. Mignonac-Mondon, *Bull. Soc. Chim. France*, 4436 (1970).

(9) H. Brintzinger, K. Pfannstiel and H. Koddebusch, *Angew. Chem.*, **60**, 312 (1948).

(10) H. Chartier and R. Vessiére, *Ann. Chim.*, 313 (1969).

(11) A. M. Birks and G. F. Wright, *J. Am. Chem. Soc.*, **62**, 2421 (1940).

(12) T. Posner and O. Unverdorben, *Ann. Chem.*, **389**, 117 (1912).

(13) J. Matt, U. S. Patent 3,608,084 (Nalco Chemical Company, Chicago, Ill) (1971); *Chem. Abstr.*, **75**, 154905j (1971).

(14) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

(15) M. Cariou, *Bull. Soc., Chim. France*, 198 (1969); L. Aspart-Pascot and J. Lematre, *ibid.*, 483 (1971).

(16) A. D. Josey, C. L. Dickinson, K. C. Dewhirst and B. C. McKusic, *J. Org. Chem.*, **32**, 1941 (1967).

(17) A. N. Kost and R. S. Sagitullin, *Vestn. Mosk. Univ., Ser. Mat., Mekh., Astron., Fiz., Khim.*, **14**, 225 (1959); *Chem. Abstr.*, **53**, 21894a (1959).

(18) By De Witt Neighbours, A. L. Foster, S. M. Clarke, J. E. Miller and J. R. Bailey, *J. Am. Chem. Soc.*, **44**, 1557, 1560 (1922).

(19) M. Busch and K. Linsenmeier, *J. Prakt. Chem.*, [2] **115**, 218 (1927).

(20a) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **41**, 306 (1958); (b) P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *ibid.*, **42**, 763 (1959).

(21) A. Takamizawa and S. Hayashi, *Yakugaku Zasshi*, **83**, 313 (1963); *Chem. Abstr.*, **59**, 5147a (1963).

(22) French Patent 1,403,372 (Chemische Fabrik von Heyden, AG); *Chem. Abstr.*, **63**, 14871a (1965); H. Höhn, *Z. Chem.*, **10**, 386 (1970).

(23) E. L. Anderson, J. E. Casey Jr., L. C. Greene, J. J. Lafferty and H. E. Reiff, *J. Med. Chem.*, **7**, 259 (1964).

(24) E. Alcalde, J. de Mendoza, J. M. Garcia-Marquina, C. Almera and J. Elquero, *J. Heterocyclic Chem.*, **11**, 423 (1974).

(25) I. I. Grandberg, Din Vai-Py, V. I. Shchegolova and A. N. Kost, *J. Gen. Chem. USSR*, **31**, 1770 (1961); *Chem. Abstr.*, **55**, 25921a (1961).

(26) E. Mohr, *J. Prakt. Chem.*, **79**, 1 (1909).

(27) I. Hori and M. Igarashi, *Bull. Chem. Soc. Japan*, **44**, 2856 (1971).

(28) L. Aspart-Pascot, J. Lematre and A. Sournia, *C. R. Acad. Sci. Ser. C*, **272**, 103 (1971).

(29) H. Dorn and A. Zubek, *Z. Chem.*, **5**, 456 (1956).

(30) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

(31) O. Seidel, *J. Prakt. Chem.*, **58**, 150 (1898).