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# Synthesis and Reaction of 1-(N,N-Disubstituted amino)pyrazoles[1]

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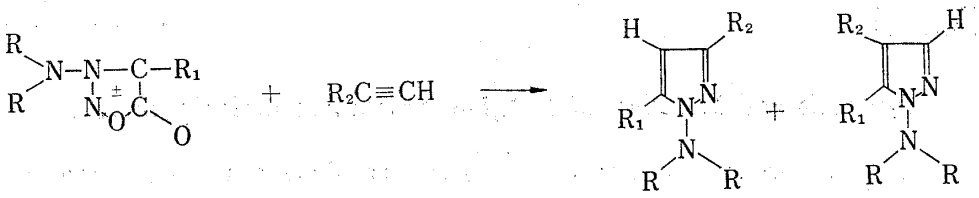
Some 1-(N,N-disubstituted amino)pyrazoles were synthesized by 1,3-dipolar cycloaddition of 3-(N,N-disubstituted amino)sydnones with acetylenes. Arylacetylenes gave 3-arylpyrazoles preferentially. The structures were determined by ultraviolet and nuclear magnetic resonance spectroscopy, and further confirmed by catalytic hydrogenolysis and mass spectroscopy. Nitration and halogenation of 3-phenyl-1-aminopyrazoles occurred smoothly at C-4 first and at C-5 subsequently.

Despite the extensive studies of the chemistry of pyrazoles,[3] relatively little has been known about 1-aminopyrazoles.[4] This paper describes the synthesis and some electrophilic substitution reactions of 1-(N,N-disubstituted amino)pyrazoles.

Huisgen, *et al.*[5] obtained 1,3-diphenylpyrazole by 1,3-dipolar cycloaddition of 3-phenylsydnone with phenylacetylene (**2a**) in chlorobenzene at 120°. In the course of synthetic studies of heterocyclic compounds, we attempted the reaction of 3-dimethylaminosydnone[6] (**1a**) with **2a** under the reaction condition of Huisgen's method. But the reaction did not proceed and the starting materials were completely recovered. However, when the mixture was heated over 200° in tetrahydronaphthalene, **1a** was consumed in several hours, and after chromatographic separation, 1-dimethylamino-3-phenylpyrazole (**3a**) was obtained in a 60% yield. Isomeric 1-dimethylamino-4-phenylpyrazole (**4a**) was also produced in a small amount but could not be isolated in a pure form. The structure of **3a** was confirmed on the basis of ultraviolet (UV)[7] and nuclear magnetic resonance (NMR)[8] spectral data: UV (MeOH) 252 nm (the typical absorption of a phenylpyrazole, $\varepsilon=17000$); NMR ($CCl_4$) $\delta$ 7.1—8.1 (6H, multiplet, aromatic protons at C-5 and on the benzene ring), 6.40 (1H, doublet, $J=2.5$ Hz, $C_4$–H), 2.89 ppm (6H, singlet, $Me_2N$). On the other hand the NMR spectrum of the crude sample of **4a** showed no signal in the region of 6 to 7 ppm, revealing that the C-4 of the pyrazole ring was occupied by a phenyl substituent.[8] Similar results were obtained by use of 3-morpholinosydnone (**1b**) or 3-piperidinosydnone (**1c**) in place of **1a**, and also by use of *p*-chlorophenylacetylene (**2b**), *p*-tolylacetylene (**2c**) or *n*-1-octyne (**2d**) in place of **2a** (Chart 1). In all cases 3-substituted pyrazoles (**3b**—**f**) were predominantly formed and isolated by column chromatography on silica gel in 22—50% yields. The corresponding 4-substituted isomers were also detected, generally in a small amount, on thin-layer chromatograms of the reaction

1) A part of this work was presented at the 3rd Symposium of Heterocyclic Compounds, Tokyo, November 1970.
2) Location: *Juso-Honmachi, Yodogawa-ku, Osaka*; *a*) Present address: *Faculty of Pharmaceutical Sciences, Toyama University, Gofuku, Toyama.*
3) A.R. Katritzky and A.J. Boulton (eds.), "Advances in Heterocyclic Chemistry," Vol. 6, Academic Press, Inc., New York, N. Y., 1966, pp. 347—429.
4) R.J. Harder, U.S. Patent 3207763 (1965) [*C. A.*, **63**, 18096 (1965)]; G. Adembri, F. Ponticelli, and P. Tedeschi, *J. Heterocyclic Chem.*, **9**, 1219 (1972); A.A. Achrem and A.M. Moiseenkov, *J. Parkt. Chem.*, **314**, 31 (1972).
5) R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.*, **101**, 536 (1968).
6) K. Masuda and Y. Imashiro, Japan. Patent 6016 (1970) [*C. A.*, **72**, 369 (1970)]. Other 3-aminosydnones (**1b**—**f**) were also prepared according to the method described in this patent.
7) D. Dal Monte Casoni, A. Mangini, and R. Passerini, *Gazz. Chim. Ital.*, **86**, 797 (1956).
8) L.G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).



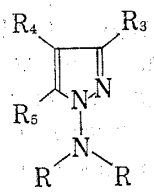
1 2 3 4

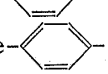
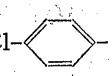
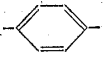
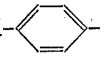
| | $N\langle^{R}_{R}$ | $R_1$ | $R_2$ |
|---|---|---|---|
| **a** | $NMe_2$ | H | $C_6H_5$ |
| **b** |  | H | Cl-  |
| **c** |  | H | Me-  |
| **d** | $NMe_2$ | Me | n-hexyl |
| **e** | $NMe_2$ | $CH_2N$  | |
| **f** | $NMe_2$ | $CH_2NMe_2$ | |

| | $N\langle^{R}_{R}$ | $R_1$ | $R_2$ |
|---|---|---|---|
| **a** | $NMe_2$ | H | $C_6H_5$ |
| **b** | $NMe_2$ | H | Cl-  |
| **c** | $NMe_2$ | H | Me-  |
| **d** | $NMe_2$ | H | n-hexyl |
| **e** |  | H | $C_6H_5$ |
| **f** |  | H | Cl-  |
| **g** | $NMe_2$ | Me | $C_6H_5$ |
| **h** | $NMe_2$ | Me | Cl-  |
| **i** | $NMe_2$ | $CH_2N$  | $C_6H_5$ |
| **j** | $NMe_2$ | $CH_2N$  | Cl-  |
| **k** | $NMe_2$ | $CH_2NMe_2$ | $C_6H_5$ |

Chart 1

TABLE I. 1-(Disubstituted amino)pyrazoles (3 and 4)



| Compd. No. | $N\langle^{R}_{R}$ | $R_3$ | $R_4$ | $R_5$ | mp, °C (bp, °C/mmHg) | Yield[a] % | NMR:[b] $C_4$–H, $\delta$ ppm ($J$, Hz) | UV: $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) |
|---|---|---|---|---|---|---|---|---|
| **3a** | $NMe_2$ | $C_6H_5$ | H | H | 35—36 (123/3.7) | 60 | 6.40 (d, $J$=2.5) | 252 (17000) |
| **4a**[c] | $NMe_2$ | H | $C_6H_5$ | H | (117—119/2.2) | — | | |
| **3b** | $NMe_2$ | Cl-  | H | H | 45—48 (115—116/0.65) | 23 | 6.21 (d, $J$=2.5) | |
| **3c** | $NMe_2$ | Me-  | H | H | (134—137/5.5) | 32 | 6.23 (d, $J$=2.5) | |
| **3d** | $NMe_2$ | *n*-hexyl | H | H | (84—85/2) | 50 | 5.78 (d, $J$=2.5) | |
| **3e** |  | $C_6H_5$ | H | H | 94—95 | 22 | 6.32 (d, $J$=2.5) | 252.5 (17500) |
| **3f** |  | Cl-  | H | H | 85—89 | 24 | 6.28 (d, $J$=2.5) | |
| **4f** |  | H | Cl-  | H | 108—112 | 1 | | |
| **3g** | $NMe_2$ | $C_6H_5$ | H | Me | 54—56 | 81 | 6.08 (s) | 253 (16700) |
| **4g** | $NMe_2$ | H | $C_6H_5$ | Me | (129/3) | 10 | | 245 (13500) |
| **3h** | $NMe_2$ | Cl-  | H | Me | 83—85 | 30 | 6.02 (s) | |

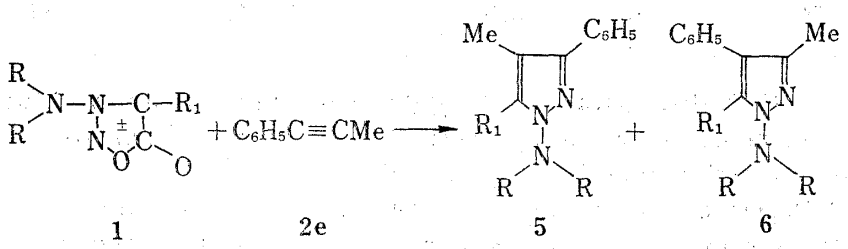
| Compd. No. | $N\langle^{R}_{R}$ | $R_3$ | $R_4$ | $R_5$ | mp, °C (bp, °C/mmHg) | Yield[a] % | NMR:[b] $C_4$-H, $\delta$ ppm ($J$, Hz) | UV: $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) |
|---|---|---|---|---|---|---|---|---|
| **4h** | $NMe_2$ | H | Cl-C$_6$H$_4$- | Me | 84—85 | 4 | | |
| **3i** | $NMe_2$ | $C_6H_5$ | H | $CH_2N$O | 81—84 | 34 | 6.22 (s) | 253 (17600) |
| **4i** | $NMe_2$ | H | $C_6H_5$ | $CH_2N$O | 82—84 | 2 | | 246 (13300) |
| **3j**[d] | $NMe_2$ | Cl-C$_6$H$_4$- | H | $CH_2N$O | 224—226 (decomp.) | 12 | 6.83 (s) | |
| **4j** | $NMe_2$ | H | Cl-C$_6$H$_4$- | $CH_2N$O | 119—120 | 2 | | |
| **3k**[d] | $NMe_2$ | $C_6H_5$ | H | $CH_2NMe_2$ | 211—213 (decomp.) | 12 | 6.70 (s) | |

*a*) Both products, **3** and **4**, were separated from the reaction mixture by column chromatography on silica gel, and then purified by distillation or recrystallization.
*b*) solvent: **3j** and **3k**; $D_2O$. others; $CCl_4$
*c*) IR and NMR spectra of **4a** showed the presence of some impurities
*d*) monohydrochloride

mixtures and only one compound, 4-(*p*-chlorophenyl)-1-piperidinopyrazole (**4f**), was isolated in a yield lower than 1%. On the other hand, the formation of the 4-substituted isomers were considerably increased in the reactions of 4-substituted 3-dimethylaminosydnones (**1d—f**) with **2a** or **2b**, affording 4-arylpyrazoles (**4g—j**) in 2—10% yields after chromatographic separation. In these cases, the yields of 3-arylpyrazoles (**3g—k**) varied in a wide range of 12—81% (Table I). Structures of these 3,5-disubstituted pyrazoles (**3g—k**) and their 4,5-disubstituted isomers (**4g—j**) were determined by NMR spectroscopy in the same manner as described in the case of **3a** and **4a**.

Treatment of 1-phenyl-1-propyne (**2e**), an unsymmetrically-disubstituted acetylene, with aminosydnones (**1a—e**) gave an about 1:1 mixture of the corresponding 4-methyl-3-phenylpyrazoles (**5**) and 3-methyl-4-phenylpyrazoles (**6**). Thus the proportions of the yields of 3- and 4-arylpyrazoles depend markedly on the kinds of acetylenes in good accord with the results obtained by Huisgen, *et al.* The structures of **5** and **6** were assigned by inspection of their UV spectra. As shown in Table I, 1-(N,N-disubstituted amino)-3-phenylpyrazoles exhibited the maximum absorptions at 252—253 nm in their UV spectra, while the isomeric 4-phenylpyrazoles at 245—246 nm. Therefore the compounds (**5**) whose maximum absorptions appeared at 250—252 nm were assigned to 3-phenylpyrazoles and their counterparts (**6**) to 4-phenyl isomers (Table II).

The reactions of diphenylacetylene (**2f**), a symmetrically-disubstituted acetylene, with aminosydnones (**1a—e**) gave 3,4-diphenylpyrazoles (**7a—e**) as the sole product (Table III).

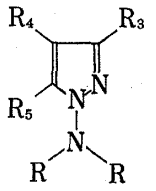


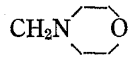

1 2e 5 6

| | a | b | c | d | e |
|---|---|---|---|---|---|
| $N\langle^{R}_{R}$: | $NMe_2$ | N O | N | $NMe_2$ | $NMe_2$ |
| $R_1$ : | H | H | H | Me | $CH_2N$O |

Chart 2

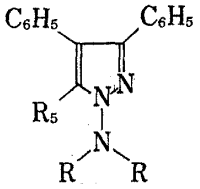
Table II. 1-(Disubstituted amino)pyrazoles (**5** and **6**)

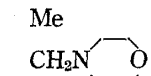


| Compd. No. | $N^{R}_{R}$ | $R_3$ | $R_4$ | $R_5$ | mp, °C (bp, °C/mmHg) | Yield % | UV: $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) |
|---|---|---|---|---|---|---|---|
| **5a** | $NMe_2$ | $C_6H_5$ | Me | H | (137/6) | 12 | 251(12400) |
| **6a** | $NMe_2$ | Me | $C_6H_5$ | H | (124—125/3) | 10 | 245(12000) |
| **5b** |  | $C_6H_5$ | Me | H | 129—132 | 6 | 251(13500) |
| **6b** |  | Me | $C_6H_5$ | H | — | — | 245(12700) |
| **5c** |  | $C_6H_5$ | Me | H | 97—99 | 6 | 252(13700) |
| **6c** |  | Me | $C_6H_5$ | H | — | — | 246(12800) |
| **5d** | $NMe_2$ | $C_6H_5$ | Me | Me | 43—47 (133/2.7) | 17 | 250(11700) |
| **6d** | $NMe_2$ | Me | $C_6H_5$ | Me | (136/2.5) | 29 | 241(11200) |
| **6e**[a] | $NMe_2$ | Me | $C_6H_5$ |  | 204—212 (decomp.) | — | 243(10200) |

a) monohydrochloride

Table III. 1-(Disubstituted amino)-3,4-diphenylpyrazoles (**7**)

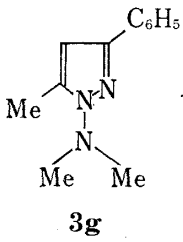


| Compd. No. | $N^{R}_{R}$ | $R_5$ | mp, °C (bp, °C/mmHg) | Yield % |
|---|---|---|---|---|
| **7a** | NMe | H | 54—61 (202/8.5) | 18 |
| **7b** |  | H | 107—109 | 12 |
| **7c** |  | H | 96—101 | — |
| **7d** | $NMe_2$ | Me | 121—123 | 56 |
| **7e** | $NMe_2$ |  | 118—120 | 12 |

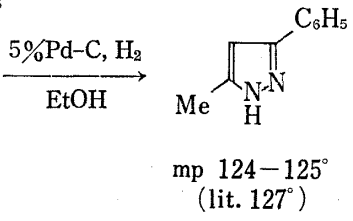
Structures of 1-(N,N-disubstituted amino)pyrazoles obtained above were further confirmed by their mass spectra and catalytic hydrogenolysis of 1-dimethylamino-5-methyl-3-phenylpyrazole (**3g**) to 5(3)-methyl-3(5)-phenylpyrazole.[9]

Nishiwaki[10] reported that in the mass spectrum of 1-ethyl-3,5-dimethylpyrazole, the base peak was the *m/e* 96 species which was produced by loss of ethylene from the molecular ion (Chart 4). This elimination proceeds through the proton transfer from the methyl-carbon of the ethyl group to the ring-nitrogen.

9) B. Sjollema, *Ann.*, **279**, 248 (1894).
10) T. Nishiwaki, *J. Chem. Soc.* (*B*), **1967**, 885.

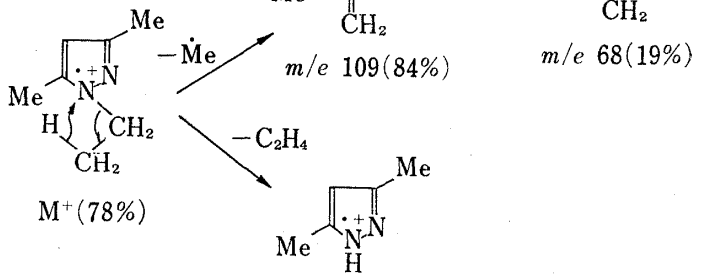



3g




mp 124–125°
(lit. 127°)

Chart 3




M+(78%)

m/e 109(84%)

m/e 68(19%)

m/e 96(100%)

Chart 4

Table IV. High Resolution Mass Spectrum of 1-Dimethylamino-3-phenylpyrazole (3a)

| m/e | Relative abundance (%) | Observed | Calculated |
|---|---|---|---|
| 187 | 100 | 187.114 | 187.110 ($C_{11}H_{13}N_3$) |
| 172 | 18 | 172.083 | 172.087 ($C_{10}H_{10}N_3$) |
| 144 | 60 | 144.067 | 144.068 ($C_9H_8N_2$) |
| 119 | 11 | 119.064 | 119.060 ($C_7H_7N_2$) |
| 118 | 52 | 118.066 | 118.065 ($C_8H_8N$) |
| 117 | 19 | 117.055 | 117.057 ($C_8H_7N$) |
| 115 | 23 | 115.053 | 115.054 ($C_9H_7$) |
| 103 | 16 | 103.041 | 103.042 ($C_7H_5N$) |
| 89 | 13 | 89.040 | 89.039 ($C_7H_5$) |
| 83 | 33 | 83.062 | 83.060 ($C_4H_7N_2$) |
| 77 | 19 | 77.035 | 77.039 ($C_6H_5$) |
| 63 | 18 | 63.011 | 63.010 ($C_4HN$) |
| 57 | 20 | 57.058 | 57.057 ($C_3H_7N$) |

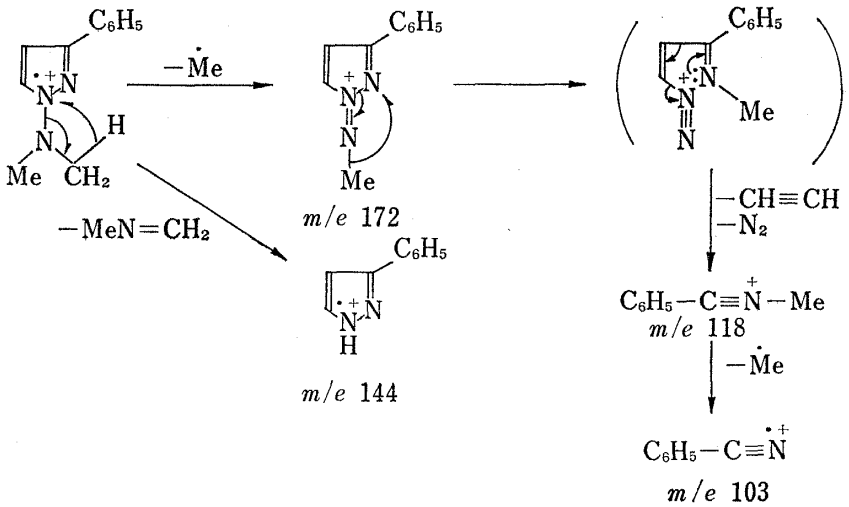



Chart 5

TABLE V. Mass Spectra[a] of 1-(N,N-Disubstituted amino)pyrazoles

| Compd. No. | | Molecular ion ($M^+$) |  8 | $Ar-C\equiv\overset{+}{N}-CH_3$ 9 | Main other ions ($m/e \geqq 77$) |
|---|---|---|---|---|---|
| **3b** | *m/e* | 223, 221 | 180, 178 | 154, 152 | 151, 149, 137, 115, 114, 113, 111, 83 |
| | R.I. | 31, 93 | 22, 65 | 28, 89 | 21, 20, 22, 21, 26, 24, 24, 100 |
| **3c** | *m/e* | 201 | 158 | 132 | 187, 157, 144, 118, 117, 77 |
| | R.I. | 100 | 43 | 60 | 47, 21, 26, 36, 22, 25 |
| **3e** | *m/e* | 229 | 144 | | 230, 172, 171, 145, 143, 117, 115, 103, 89, 86, 85, 77 |
| | R.I. | 62 | 51 | | 42, 100, 23, 43, 23, 50, 56, 25, 26, 27, 25, 32 |
| **3f** | *m/e* | 263, 261 | 180, 178 | | 84, 83 |
| | R.I. | 14, 42 | 33, 100 | | 62, 88 |
| **3g** | *m/e* | 201 | 158 | 118 | 77 |
| | R.I. | 58 | 100 | 35 | 26 |
| **3h** | *m/e* | 237, 235 | 194, 192 | 154, 152 | 193 |
| | R.I. | 21, 69 | 34, 100 | 9, 25 | 21 |
| **4f** | *m/e* | 263, 261 | 180, 178 | | 84, 83 |
| | R.I. | 27, 81 | 33, 100 | | 28, 61 |
| **4g** | *m/e* | 201 | 158 | | 159, 157, 130, 129, 115, 91, 89, 77 |
| | R.I. | 71 | 100 | | 23, 22, 45, 20, 29, 22, 23, 25 |
| **4h** | *m/e* | 237, 235 | 194, 192 | | 220, 115, 43 |
| | R.I. | 25, 74 | 33, 92 | | 21, 20, 100 |
| **5a** | *m/e* | 201 | 158 | 118 | 157, 83, 77 |
| | R.I. | 100 | 27 | 100 | 41, 42, 38 |
| **5b** | *m/e* | 243 | 158 | | 186, 157, 128, 117, 104, 86, 77 |
| | R.I. | 100 | 62 | | 38, 52, 22, 30, 20, 21, 35 |
| **5c** | *m/e* | 241 | 158 | | 159, 157, 130, 129, 128, 114, 113, 97, 84, 83, 82, 77 |
| | R.I. | 86 | 100 | | 21, 58, 32, 22, 21, 29, 22, 21, 41, 39, 27, 39 |
| **5d** | *m/e* | 215 | 172 | 118 | 216, 171, 131, 77 |
| | R.I. | 98 | 100 | 53 | 21, 94, 21, 35 |
| **6a** | *m/e* | 201 | 158 | | 130, 117, 116, 91, 90, 89, 77 |
| | R.I. | 60 | 28 | | 22, 35, 30, 25, 26, 21, 20 |
| **6d** | *m/e* | 215 | 172 | | 173, 171, 130, 115 |
| | R.I. | 50 | 100 | | 21, 24, 24, 28 |
| **7a** | *m/e* | 263 | 220 | 118 | 219, 189, 117, 116, 102, 90, 89, 77 |
| | R.I. | 78 | 27 | 100 | 34, 21, 34, 48, 23, 27, 33, 33 |
| **7b** | *m/e* | 305 | 220 | | 306, 248, 221, 219, 191, 189, 174, 165, 117, 116, 115 |
| | R.I. | 100 | 70 | | 27, 27, 20, 54, 23, 30, 23, 25, 39, 27, 20 |
| | *m/e* | | | | 103, 102, 99, 90, 89, 86, 77 |
| | R.I. | | | | 25, 30, 33, 21, 36, 34, 27 |
| **7c** | *m/e* | 303 | 220 | | 304, 219 |
| | R.I. | 100 | 59 | | 24, 27 |
| **7d** | *m/e* | 277 | 234 | 118 | 278, 235, 233 |
| | R.I. | 97 | 100 | 31 | 25, 25, 37 |

a) Intensities are given in per cent of base peak and listed only if they are greater than 20%.

We also expected a similar fragmentation for 1-(N,N-disubstituted amino)pyrazoles to give 1-deaminated ions (**8**) (see Table V). In this case it is supposed that the proton transfer takes place from the N-methyl-carbon to the ring-nitrogen. First the high resolution mass spectrum of **3a** was studied as a representative. The results were summarized in Table IV. A possible fragmentation was shown in Chart 5.

Mass spectral data of other compounds (**3**—**7**) supported this fragmentation (Table V). While 1-deaminated ions (**8**) were commonly observed in the spectra of these compounds,[11]

11) 1-Morpholino and 1-piperidinopyrazoles gave the ions ($M^+-85$) and ($M^+-83$), respectively, via a similar proton transfer as described in the case of **3a**.

additional ion species (**9**) (see Table V) were found in those of 1-dimethylamino-3-arylpyrazoles. The species were probably produced by expulsion of a methyl radical, transfer of the second methyl radical to N-2 accompanying the rupture of $N_1$–$N_2$ bond and expulsion of acetylene and nitrogen.

Subsequently, some electrophilic substitution reactions were undertaken toward the pyrazole ring of 1-substituted aminopyrazoles prepared by the above reactions. Nitration of **3a** with nitric acid proceeded very smoothly at room temperature to give 1-dimethylamino-4,5-dinitro-3-phenylpyrazole (**10**), the structure of which was determined on the basis of the NMR and mass spectral data: NMR (in ($CCl_4$) $\delta$ 7.3—7.8 (5H, multiplet, aromatic protons), 2.93 ppm (6H, singlet, $NMe_2$); Mass Spectrum *m/e*: 277 ($M^+$), 77 ($C_6H_5^+$), 51 ($C_4H_3^+$). It has been shown that the 5-position of a pyrazole generally resists nitration, because it forms a protonated cation in an acidic medium.[12] When a nitro group is substituted at the 4-position, further nitration at the 5-position would be more difficult because of the added effect of the electron-withdrawing nitro group. The fact that 4,5-dinitro derivative was formed in the above reaction under such a mild condition can be interpreted by a potent electron donating effect of the 1-dimethylamino group. When 1-morpholino-3-phenylpyrazole (**3e**) was treated with nitric acid at 0°, 1-morpholino-4-nitro-3-phenylpyrazole (**11**) was obtained as colorless crystals. In an attempt to establish the substituted position of the nitro group, **11** was subjected to catalytic reduction. Column chromatography of the reaction mixture afforded two products, 4-amino-3-phenylpyrazole (**12**) and 4-amino-1-morpholino-3-phenylpyrazole (**13**). While, in the NMR spectra, the proton at the 5-position of **12** appeared at 7.0—7.9 ppm overlapping with phenyl signals at the 3-position,[13] **13** showed a clear-cut singlet at 7.06 ppm due to the proton at the 5-position.

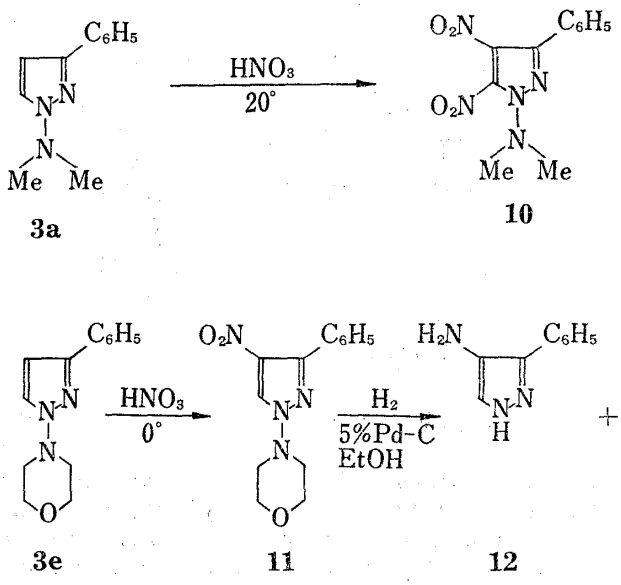



Chart 6

Halogenation of 1-(N,N-disubstituted amino)-3-phenylpyrazoles also occurred preferentially at the 4-position and subsequently at the 5-position. Thus chlorination of **3a** with molecular chlorine or N-chlorosuccinimide gave a mixture of its 4-chloro and 4,5-dichloro derivatives (**14** and **15**), which were isolated by column chromatography and purified by distillation under reduced pressure. The NMR spectrum of **14** exhibited a singlet at 7.40 ppm

12) C.L. Habraken, P. Cohen-Fernandes, S. Balian, and K.C. van Erk, *Tetrahedron Letters*, **1970**, 479; J. W. A.M. Janssen, H.J. Koeners, C.G. Cruse, and C.L. Habraken, *J. Org. Chem.*, **38**, 1777 (1973).

13) The possible isomer, 5-amino-3-phenylpyrazole, shows a singlet at 5.94 ppm in the NMR spectrum due to the proton at the 4-position; L.G. Tensmeyer and C. Ainworth, *J. Org. Chem.*, **31**, 1878 (1966).

due to the proton at C-5. Similarly **3e** was chlorinated with N-chlorosuccinimide to give 4-chloro and 4,5-dichloro derivatives (**16** and **17**). When **3a** was treated with an equimolar amount of N-bromosuccinimide in carbon tetrachloride under reflux, 4-bromo-1-dimethylamino-3-phenylpyrazole (**18**) was obtained as a colorless oil in an almost quantitative yield. When **3g** was treated with the same reagent, bromination occurred first at the 4-position and subsequently at the methyl group of the 5-position, giving rise to the formation of two products, 4-bromo-1-dimethylamino-5-methyl-3-phenylpyrazole (**19**) and 4-bromo-5-bromomethyl-1-dimethylamino-3-phenylpyrazole (**20**), which were isolated from the reaction mixture by column chromatography. Compounds prepared in this study were examined for biological activities and some of them exhibited analgetic and antipyretic activities, details of which will be published elsewhere by pharmacologists of our division.

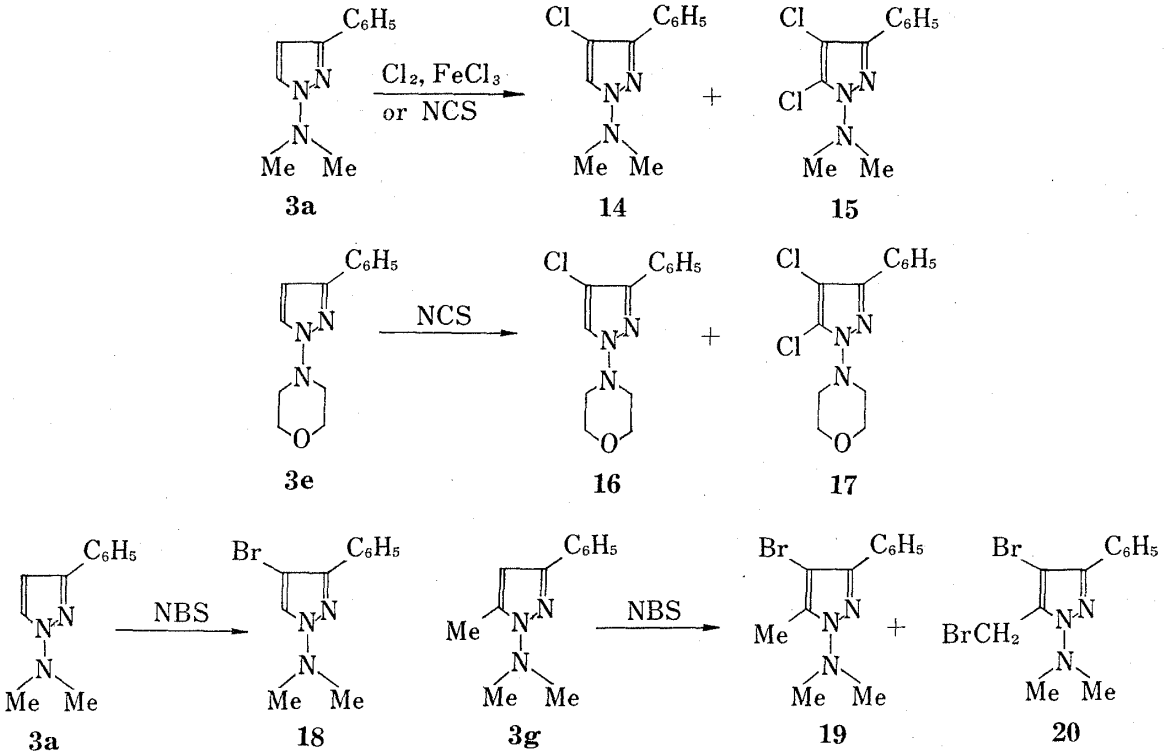



Chart 7

## Experimental[14]

**Preparation of 1-(N,N-Disubstituted amino)pyrazoles** (3—7)——The mixture of 0.1 mole of 3-(N,N-disubstituted amino)sydnone (1) and 0.2 mole of substituted acetylene (2) in 100 ml of tetrahydronaphthalene was heated under reflux for 5 hr, and then concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene–AcOEt to give 1-(N,N-disubstituted amino)pyrazoles (3—7). The data of elemental analyses were shown in Table VI.

**Hydrogenolysis of 1-Dimethylamino-5-methyl-3-phenylpyrazole** (3g)——To a suspension of 10 g of 5% Pd–C in 200 ml of EtOH was added a solution of 1.4 g of **3g** in 20 ml of EtOH, and the mixture was shaken under a hydrogen atmosphere at room temperature. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. To the residue were added water and $K_2CO_3$, and the resulting precipitates were extracted with AcOEt. The extract was washed with water, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residual solid was recrystallized from cyclohexane to give 0.55 g of 5(3)-methyl-3(5)-phenylpyrazole as colorless crystals, mp 124—125°. This compound was identified with an authentic sample.[9]

14) Melting and boiling points were uncorrected. Infrared (IR) spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard. UV spectra were taken with a Perkin-Elmer 450 spectrophotometer.

TABLE VI. Elemental Analyses of 1-(N,N-Disubstituted amino)pyrazoles (3—7)

| Compd. No. | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|
| **3a** | $C_{11}H_{13}N_3$ | 70.56 | 7.00 | 22.44 | 70.79 | 6.90 | 22.38 |
| **3b** | $C_{11}H_{12}N_3Cl$ | 59.59 | 5.46 | 18.96 | 59.77 | 5.43 | 19.05 |
| **3c** | $C_{12}H_{15}N_3$ | 71.63 | 7.51 | 20.88 | 71.87 | 7.54 | 21.22 |
| **3d** | $C_{11}H_{21}N_3$ | 67.64 | 10.84 | 21.52 | 68.00 | 11.05 | 21.51 |
| **3e** | $C_{13}H_{15}ON_3$ | 68.10 | 6.59 | 18.33 | 68.46 | 6.63 | 18.64 |
| **3f** | $C_{14}H_{16}N_3Cl$ | 64.23 | 6.16 | 16.05 | 64.33 | 6.17 | 16.17 |
| **3g** | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | 71.74 | 7.43 | 20.37 |
| **3h** | $C_{12}H_{14}N_3Cl$ | 61.14 | 5.99 | 17.83 | 61.07 | 5.97 | 18.05 |
| **3i** | $C_{16}H_{22}ON_4$ | 67.11 | 7.74 | 19.56 | 66.91 | 7.65 | 19.49 |
| **3j** | $C_{16}H_{21}ON_4Cl \cdot HCl$ | 53.79 | 6.21 | 15.68 | 53.65 | 6.34 | 15.80 |
| **3k** | $C_{14}H_{20}N_4 \cdot HCl$ | 59.88 | 7.54 | 19.95 | 60.00 | 7.42 | 20.04 |
| **4f** | $C_{14}H_{16}N_3Cl$ | 64.23 | 6.16 | 16.05 | 64.56 | 6.18 | 15.78 |
| **4g** | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | 71.96 | 7.43 | 20.77 |
| **4h** | $C_{12}H_{14}N_3Cl$ | 61.14 | 5.99 | 17.83 | 61.13 | 6.03 | 18.14 |
| **4i** | $C_{16}H_{22}ON_4$ | 67.11 | 7.74 | 19.56 | 67.17 | 7.58 | 19.62 |
| **4j** | $C_{16}H_{21}ON_4Cl$ | 59.91 | 6.60 | 17.47 | 60.03 | 6.63 | 17.72 |
| **5a** | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | 71.67 | 7.54 | 20.35 |
| **5b** | $C_{14}H_{17}ON_3$ | 69.11 | 7.04 | 17.27 | 69.10 | 7.12 | 17.15 |
| **5c** | $C_{15}H_{19}N_3$ | 74.65 | 7.94 | 17.41 | 74.60 | 7.98 | 17.58 |
| **5d** | $C_{13}H_{17}N_3$ | 72.52 | 7.96 | 19.52 | 72.56 | 7.80 | 19.42 |
| **6a** | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | 71.98 | 7.61 | 20.55 |
| **6b** | $C_{14}H_{17}ON_3$ | 69.11 | 7.04 | 17.27 | 69.61 | 7.08 | 17.08 |
| **6c** | $C_{15}H_{19}N_3$ | 74.65 | 7.94 | 17.41 | 74.89 | 7.65 | 17.09 |
| **6d** | $C_{13}H_{17}N_3$ | 72.52 | 7.96 | 19.52 | 72.41 | 7.97 | 19.40 |
| **6e** | $C_{17}H_{24}ON_4 \cdot HCl$ | 60.61 | 7.48 | 16.63 | 60.38 | 7.51 | 16.63 |
| **7a** | $C_{17}H_{17}N_3$ | 77.53 | 6.51 | 15.96 | 77.87 | 6.56 | 15.55 |
| **7b** | $C_{19}H_{19}ON_3$ | 74.73 | 6.27 | 13.76 | 75.02 | 6.34 | 13.81 |
| **7c** | $C_{20}H_{21}N_3$ | 79.17 | 6.98 | 13.85 | 79.28 | 6.94 | 13.32 |
| **7d** | $C_{18}H_{19}N_3$ | 77.94 | 6.91 | 15.15 | 77.65 | 6.90 | 15.03 |
| **7e** | $C_{22}H_{26}ON_4$ | 72.90 | 7.23 | 15.46 | 73.42 | 7.23 | 15.60 |

**1-Dimethylamino-4,5-dinitro-3-phenylpyrazole (10)**——To 200 ml of nitric acid ($d=1.38$) was added 5.7 g of 1-dimethylamino-3-phenylpyrazole (**3a**). The mixture was stirred for 2.5 hr at 20°, and then poured into 2 liters of water. After neutralization with $NaHCO_3$, the resulting precipitates were extracted with AcOEt. The extract was washed with water, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give 2.4 g of **10**. Recrystallization from hexane gave 1.7 g (20%) of yellow crystals, mp 97—99°. *Anal.* Calcd. for $C_{11}H_{11}O_4N_5$: C, 47.65; H, 4.00; N, 25.26. Found: C, 47.90; H, 3.85; N, 25.81.

**1-Morpholino-4-nitro-3-phenylpyrazole (11)**——To 20 ml of nitric acid ($d=1.38$) was added 2.0 g of 1-morpholino-3-phenylpyrazole (**3e**) under stirring and ice-cooling. After a while the reaction mixture turned to a clear solution, and then precipitates were formed again. After 30 min, the precipitates were collected by filtration, washed with water, dried over $P_2O_5$ and recrystallized from 100 ml of MeOH to give 1.6 g (67%) of **11** as colorless crystals, mp 166—168°. *Anal.* Calcd. for $C_{13}H_{14}O_3N_4$: C, 56.91; H, 5.15; N, 20.43. Found: C, 57.27; H, 5.17; N, 20.41. NMR (in $CDCl_3$) $\delta$: 8.25 (1H, s, $C_5$-H).

**Catalytic Reduction of 1-Morpholino-4-nitro-3-phenylpyrazole (11)**——To a suspension of 10 g of 5% Pd–C in 150 ml of EtOH was added a solution of 1.0 g of **11** in 60 ml of EtOH, and the mixture was shaken under a hydrogen atmosphere at room temperature for 6 hr. After the catalyst was removed by filtration, the solvent was evaporated under reduced pressure. To the residue were added water and $K_2CO_3$, and the resulting precipitates were extracted with AcOEt. The extract was washed with water, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene–AcOEt (1: 3) to give 4-amino-3-phenylpyrazole (**12**) and 4-amino-1-morpholino-3-phenylpyrazole (**13**). The former (**12**) was converted into its monohydrochloride, which was recrystallized from iso-PrOH to give 70 mg, mp 243—245° (decomp.). *Anal.* Calcd. for $C_9H_9N_3 \cdot HCl$: C, 55.27; H, 5.15; N, 21.48. Found: C, 55.32; H, 5.54; N, 20.91. The latter (**13**) was recrystallized from cyclohexane to give 40 mg, mp 120—123°. *Anal.* Calcd. for $C_{13}H_{16}ON_4$: C, 63.90; H, 6.60; N, 22.93. Found: C, 63.96; H, 6.57; N, 22.65.

**Chlorination of 1-Dimethylamino-3-phenylpyrazole (3a)**——a) A mixture of 5.7 g of **3a** and 9.5 g of N-chlorosuccinimide in 100 ml of $CCl_4$ was heated under reflux for 3 hr. After being cooled, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give 4-chloro-1-dimethylamino-3-phenylpyrazole (**14**) and 4,5-dichloro-1-dimethylamino-3-phenylpyrazole (**15**). Both of **14** and **15** were purified by distillation under reduced pressure. **14**: bp 148° (7.5 mmHg), 1.2 g (18%). *Anal.* Calcd. for $C_{11}H_{12}N_3Cl$: C, 59.59; H, 5.46; N, 18.96. Found: C, 59.65; H, 5.52; N, 19.24. **15**: bp 152—156° (7.5 mmHg), 2.4 g (31%). *Anal.* Calcd. for $C_{11}H_{11}N_3Cl_2$: C, 51.58; H, 4.33; N, 16.41. Found: C, 51.79; H, 4.05; N, 16.52.

*b*) To a stirred, ice-cooled mixture of 1.9 g of **3a** and 1.6 g of $FeCl_3$ in 40 ml of $CH_2Cl_2$ was added a solution of 0.78 g of $Cl_2$ in 10 ml of $CH_2Cl_2$, and the mixture was stirred for 3 hr under cooling. The reaction solution was washed with dilute HCl and dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel with benzene to give 1.3 g of **14** and 0.1 g of **15**.

**Chlorination of 1-Morpholino-3-phenylpyrazole (3e)**——A mixture of 4.6 g of **3e** and 3.7 g of N-chlorosuccinimide in 50 ml of $CCl_4$ was heated under reflux for 4 hr. After being cooled, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residual solid was recrystallized from 100 ml of hexane to give 3.1 g of 4-chloro-1-morpholino-3-phenylpyrazole (**16**) as colorless crystals, mp 119—121°. *Anal.* Calcd. for $C_{13}H_{14}ON_3Cl$: C, 59.20; H, 5.35; N, 15.93. Found: C, 59.24; H, 5.22; N, 15.93. NMR (in $CDCl_3$) $\delta$: 7.45 (1H, s, $C_5$–H).

The mother liquor was concentrated under reduced pressure and the residue was chromatographed on silica gel with benzene to give 0.8 g of **16** and 0.2 g of 4,5-dichloro-1-morpholino-3-phenylpyrazole (**17**). After recrystallization from hexane, **17** gave colorless crystals, mp 89—91°. *Anal.* Calcd. for $C_{13}H_{13}ON_3Cl_2$: C, 52.35; H, 4.39; N, 14.09. Found: C, 52.52; H, 4.39; N, 14.27.

**4-Bromo-1-dimethylamino-3-phenylpyrazole (18)**——A mixture of 0.7 g of **3a** and 0.87 g of N-bromosuccinimide in 10 ml of $CCl_4$ was heated under reflux for 1 hr. After being cooled, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give 0.7 g (70%) of **18** as a colorless oil, bp 117° (4 mmHg). *Anal.* Calcd. for $C_{11}H_{12}N_3Br$: C, 49.62; H, 4.17; N, 15.79. Found: C, 49.76; H, 4.20; N, 15.85. NMR (in $CDCl_3$) $\delta$: 2.89 (6H, s, $NMe_2$), 7.56 (1H, s, $C_5$–H).

**Bromination of 1-Dimethylamino-5-methyl-3-phenylpyrazole (3g)**——A mixture of 4.05 g of **3g** and 3.6 g of N-bromosuccinimide in 50 ml of $CCl_4$ was heated under reflux for 2 hr. After being cooled, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give 5.3 g (94%) of 4-bromo-1-dimethylamino-5-methyl-3-phenylpyrazole (**19**) and 0.15 g of 4-bromo-5-bromomethyl-1-dimethylamino-3-phenylpyrazole (**20**). The former (**19**) was further purified by distillation under reduced pressure to give 4.3 g (77%) of a colorless oil, bp 134—135° (0.7 mmHg). *Anal.* Calcd. for $C_{12}H_{14}N_3Br$: C, 51.43; H, 5.04,; N 15.00. Found: C, 51.09; H, 4.99; N, 15.21. NMR (in $CCl_4$) $\delta$: 2.23 (3H, s, $C_5$–Me), 2.77 (6H, s, $NMe_2$). The structure of **20** was determined by NMR spectroscopy. NMR (in $CCl_4$) $\delta$: 2.90 (6H, s, $NMe_2$) 4.50 (2H, s, $CH_2Br$), 7.2—8.0 (5H, m, aromatic protons).

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