Propiolamidines I. Syntheses of *N,N'*-Disubstituted Phenylpropiolamidines and New Routes to 5-*N*-Substituted Amino-3-phenylisoxazoles and 5-*N*-Substituted Amino-1,3-diphenylpyrazoles

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(Received November 9, 1971)

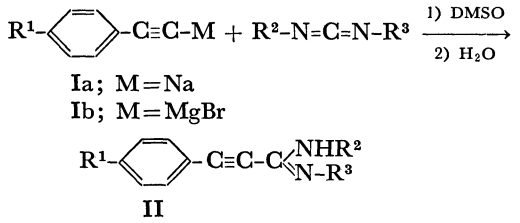
N,N'-Disubstituted phenylpropiolamidines were synthesized from phenylacetylene and carbodiimides. They were inert toward nucleophiles in a neutral or basic medium, but reactive in an acidic one. They reacted in the presence of hydrogen chloride with hydroxylamine, hydrazine, and arylhydrazines to give 5-*N*-substituted amino-3-phenylisoxazoles, 5-*N*-substituted amino-3-phenylpyrazole and 5-*N*-substituted amino-1-aryl-3-phenylpyrazoles, respectively, by nucleophilic addition followed by cyclization. The reaction mechanism is discussed on the basis of the structures of these heterocyclic compounds.

Although syntheses and reactions of amidines have been investigated in detail,[1] amidines conjugated with a carbon-carbon triple bond have not yet been reported. Even in the category of imidic acid derivatives, only two examples are known, namely substituted propiolimidates[2] and phenylpropiolamidoxime.[3]

In the present paper, syntheses and reactions of *N,N'*-disubstituted phenylpropiolamidines are described. Reaction of these amidines with hydroxylamine and hydrazines constitutes a new route to 5-*N*-substituted amino-isoxazoles and -pyrazoles, respectively.

Results and Discussion

Syntheses of N,N'-*Disubstituted Phenylpropiolamidines.* Preparation of the propiolamidines was accomplished as shown in Scheme 1. In general, sodium phenylacetylide (Ia) reacted satisfactorily with carbodiimides to give amidines (Method A), but in a few cases, the Grignard reagent (Ib) was preferred (Method B).



Scheme 1.

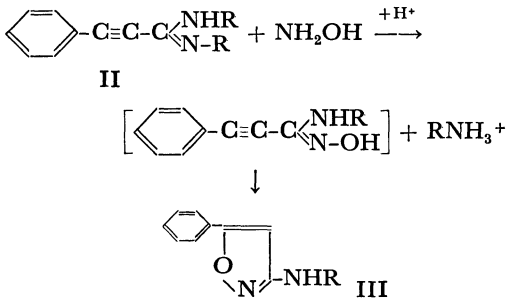
Phenylacetylene was added to metallic sodium dispersed in xylene to afford sodium phenylacetylide. The presence of tertiary amines, *e. g.*, triethylamine, *N,N*-dimethylaniline or *N,N,N',N'*-tetramethylethylenediamine, exerted a remarkable effect on the smooth formation of the acetylide at a moderate temperature in hydrocarbon solvents. The tertiary amines may stabilize the acetylide by coordination in non-polar solvents.

When dimethylsulfoxide (DMSO) was added to the sodium phenylacetylide dispersion, complex formation took place as suggested by Kriz *et al*,[4] and nucleophilic attack of the acetylide anion on carbodiimides was accelerated. No significant reaction seems to take place if no DMSO is present.

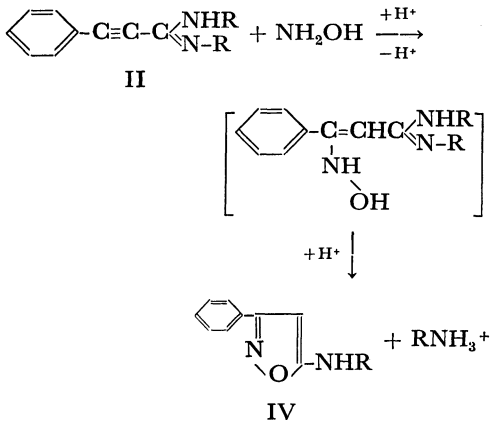
The phenylpropiolamidines were obtained as crystals, which showed infrared absorption maxima in the 2200 cm^{-1} region for acetylenic bond and near 3200 cm^{-1} attributable to N-H stretching vibration.

N,N'-Bis(*p*-nitrophenyl)phenylpropiolamidine (IIf) was not obtained from the sodium acetylide, probably because of the susceptibility of *N,N'*-bis(*p*-nitrophenyl)carbodiimide to base, but was synthesized by a reaction with the Grignard reagent of phenylacetylene.

Reactions with Hydroxylamine. Amidines are known to react with hydroxylamine in the presence



Scheme 2.



Scheme 3.

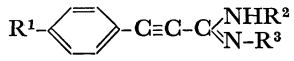
1) R. L. Shriner and F. W. Neuman, *Chem. Rev.*, **35**, 351 (1944); P. A. Smith, "Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin Inc., New York, (1966); p. 177; S. Tanimoto, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 551 (1969).

2) B. Fisher and C. A. Grob, *Helv. Chim. Acta*, **39**, 417 (1956).

3) L. Lopez, *C. R. Acad. Sci., Paris, Ser. C*, **263**, 557 (1966).

4) J. Kriz, M. J. Benes, and J. Peska, *Collect. Czech. Chem. Commun.*, **32**, 398 (1967).

TABLE 1. *N,N'*-DISUBSTITUTED PHENYLPROPIOLAMIDINES



No.	R^1	R^2	R^3	Method	Mp °C	Yield %
IIa	H	H	H	A	187—188[a]	99[c]
IIb	H			A	122—123.5	50
IIc	H	CH_3-	CH_3-	A	140.5—141	49
IId	H	CH_3O-	CH_3O-	A	122—123	65
IIe	H	Cl-	Cl-	A	153—154	31
IIf	H	NO_2-	NO_2-	B	264—265	30
IIg	H	-CH_2-	-CH_2-	A	190—191[a]	89[c]
IIh	CH_3	H	H	A	141—142[b]	88[c]
IIi	H	H		A	113—114	44
IIj	H	*n*-Bu		A	55—56	26
IIk	H	-CH_2-		A	94—95	36

a) Picrate. b) Benzoate. c) Crude viscous oil.

of acid to form amidoximes[1] and phenylpropiolamidoxime readily cyclizes to give 3-amino-5-phenylisoxazole.[3] A reaction of the propiolamidine (II) with hydroxylamine would, therefore, be presumed to proceed according to Scheme 2 to give III; but the reaction afforded a 5-*N*-substituted amino-3-phenylisoxazole (IV) and released an amine hydrochloride.

Consequently, the nucleophilic addition of hydroxylamine to the triple bond followed by cyclization might occur according to Scheme 3.

The structures of these isoxazoles (IV) were characterized on the basis of their mass and NMR spectra. The isoxazole, thus derived from IIa, was concluded to be 5-cyclohexylamino-3-phenylisoxazole (IVa), by comparison of the fragmentation pattern in the mass spectrum (Fig. 1) and the chemical shift of the C-4 proton in the NMR spectrum with those of 3-amino-5-phenyl- and 5-amino-3-phenylisoxazole.[5] As shown in Fig. 1, IVa readily released cyclohexene to give an aminoisoxazole which gave the same fragmentation pattern as that of 5-amino-3-phenylisoxazole and which was inconsistent with that of 3-amino-5-phenylisoxazole.

The NMR spectral data of IVa also supported the 5-aminoisoxazole structure. The signal at 5.26 ppm, assigned to C-4 proton of IVa, was comparable to 5-amino-3-phenylisoxazole.

The signals due to C-4 protons of 5-arylamino-3-phenylisoxazoles appeared at a reasonably lower field on account of the anisotropic effect of the phenyl ring. The chemical shift of the C-4 proton of several 5-*N*-substituted amino-3-phenylisoxazoles is given in Table 2.

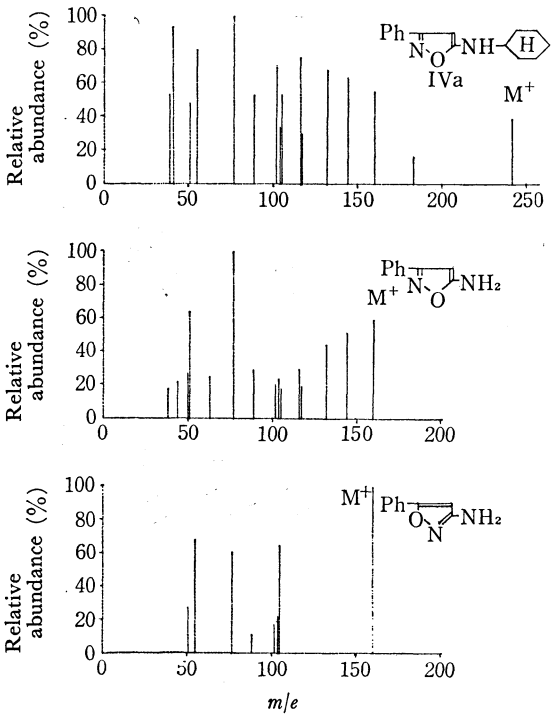
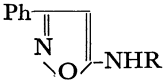
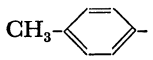
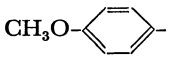


Fig. 1. Mass fragmentation patterns of 5-cyclohexylamino-3-phenylisoxazole (IVa), 5-amino-3-phenylisoxazole and 3-amino-5-phenylisoxazole.

5) I. Iwai and N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **14**, 1277 (1966).

Table 2. 5-*N*-Substituted amino-3-phenylisoxazoles

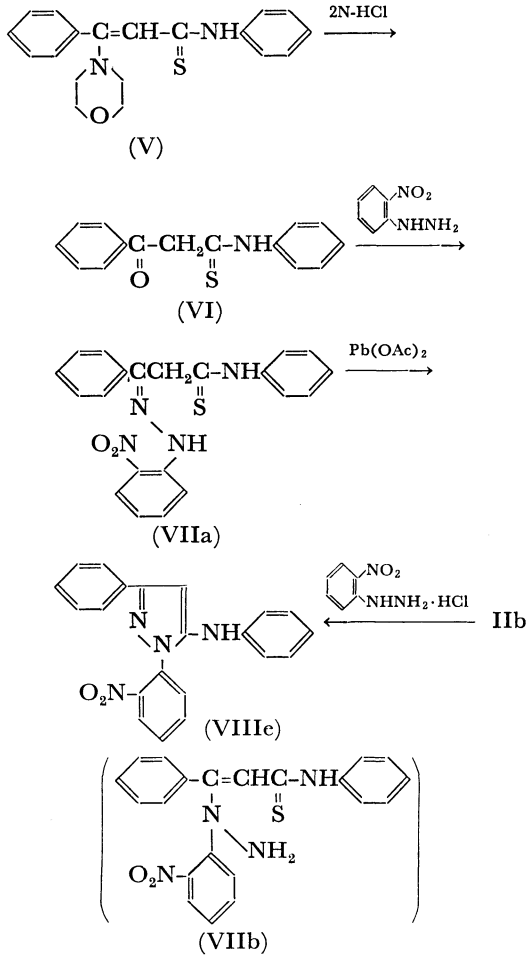


No.	R	Mp, °C	Yield %	Chemical shift of C-4 proton[a,b]
IVa		128—129.5	37	5.26
IVb		136—137[c]	55	5.85
IVc		145—146	38	5.76
IVd		150—151	53	5.65

a) δ ppm in $CDCl_3$, internal standard, TMS.
b) 3-Amino-5-phenylisoxazole: δ=6.09 ppm.
5-Amino-3-phenylisoxazole: δ=5.40 ppm.
c) Lit, mp. 137°C (Ref. 14).

Reactions with Hydrazines. It is well-known that some acetylenic compounds readily undergo addition-cyclization reactions with hydrazines to give pyrazole derivatives such as pyrazolones[6,7] and aminopyrazoles.[8]

Reactions of the propiolamidines with hydrazines were therefore carried out in a similar manner to that for the isoxazole synthesis. In the presence of sodium ethoxide, as well as under neutral conditions, phenylpropiolamidine (IIb) was chiefly recovered in a reaction of IIb with phenylhydrazine; but in the reaction with phenylhydrazine hydrochloride, the expected product, a pyrazole, was obtained together with eliminated aniline. The reaction of IIb with phenylhydrazine hydrochloride afforded predominantly a single isomer (VIIIc) of an anilinodiphenylpyrazole; namely 3-anilino-1,5-diphenyl-[9] or 5-anilino-1,3-diphenylpyrazole.[10] Both structures were assigned to the pyrazole derived from benzoylthioacetanilide and phenylhydrazine,[9,10] and exhibited the same melting point as that of VIIIc. Pocar and his co-workers[10] reported some intermediate hydrazones but presented no spectral data regarding their structures. It was supposed that these intermediates could be another structure such as VIIb in Scheme 4, whose formation was attributable to the nucleophilic attack of the α-nitrogen in phenylhydrazine at the β-acetylenic carbon and was postulated under acidic conditions[7] as in Pocar's case. We therefore confirmed the structure of an intermediate (VIIa) obtained from benzoylthioacetanilide (VI) and *o*-nitrophenylhydrazine, and compared the pyrazole cyclized from VIIa with the one derived from the amidine IIb as shown in Scheme 4.



Scheme 4.

As indicated in Table 3, the structure of the intermediate is undoubtedly the hydrazone VIIa. Consequently, the cyclization of VIIa should give 5-anilino-1-(*o*-nitrophenyl)-3-phenylpyrazole, which is completely consistent with the product from IIb and *o*-nitrophenylhydrazine hydrochloride in terms of the IR, mass and NMR spectra and melting point.

Table 3. NMR data of V, VI, and VIIa.[a]

No.	$-CH_2-$	=CH-	Enolic OH or =N-NH-	Solvent
V	—	5.91	—	$CDCl_3$
VI	4.62	6.25[b]	14.80[b]	$CDCl_3$
VIIa	4.55	—	11.05	$(CD_3)_2CO$

a) δ value from TMS.
b) Due to the presence of the enolic tautomer.

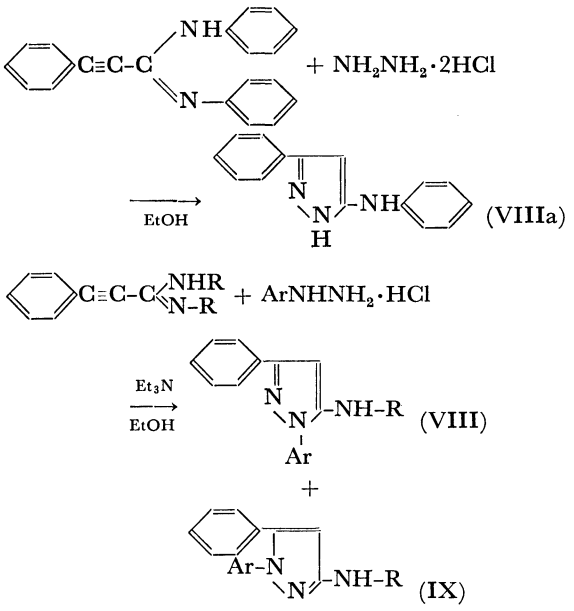
The pyrazoles homologous to 5-anilino-1,3-diphenylpyrazole were also presumed to be produced predominantly in reactions of the propiolamidines with arylhydrazines. An exception was the two isomeric pyrazoles found in the case of the reaction of *N,N'*-bis(*p*-tolyl)phenylpropiolamidine (IIc) with phenylhydrazine hydrochloride. The main product was assigned as VIIIg, by analogy with the other pyrazoles (VIII) in the reaction scheme and in spectral data, so the minor product was assumed to be 1,5-diphenyl-

6) R. v. Rosenburg, *Chem. Ber.*, **27**, 783 (1894).
7) F. G. Baddar, M. F. El-Newaihy, and M. R. Salem, *J. Chem. Soc., C*, **1969**, 836.
8) D. E. Worrall, *J. Amer. Chem. Soc.*, **59**, 933 (1937).
9) S. Hünig and K. Hübner, *Chem. Ber.*, **95**, 937 (1962).
10) D. Pocar, G. Bianchetti, and S. Maiorana, *Gazz. Chim. Ital.*, **93**, 100 (1963).

Table 4. Aminopyrazoles

No.	R	Ar	Mp, °C	Yield, %	Chemical shift of C-4 proton[a]
VIIIa		H	153.5—155[b]	49	6.32[f]
VIIIb	H		67—68.5	50	5.87
VIIIc			153.5—154.5[c]	50	6.46
VIIId		CH_3-	141—142.5	38	6.34[e]
VIIIe		NO_2 	165—166[d]	69	6.64[f]
VIIIf	CH_3O-		103—104	54	6.30
VIIIg	CH_3-		94—95	40	6.43
VIIIh	Cl-		100—101	34	6.45
IXg	CH_3-		180—181.5	7	6.24

a) δ value from TMS in $CDCl_3$. b) Lit, mp 152.5—153.5°C (Ref. 9). c) Lit, mp 153°C (Ref. 10). d) Lit, mp 164—165°C (Ref. 10). e) in CCl_4. f) in acetone-d_6.

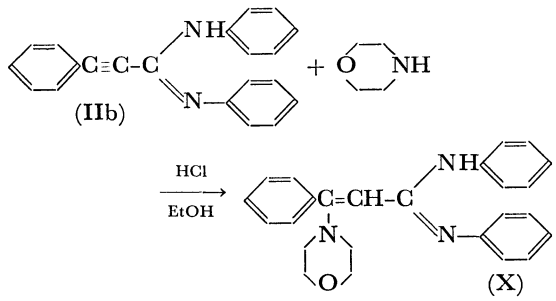


Scheme 5.

3-(*p*-toluidino)pyrazole (IXg).

Reaction Mechanism. As described above, the reactions of the propiolamidines with nucleophiles took place under acidic conditions and the acetylenic β-carbon rather than the amidino carbon was preferentially attacked. This situation was confirmed by the reaction of IIb with morpholine in the presence of hydrogen chloride resulting in addition to the triple bond giving *N*,*N*′-diphenyl-β-morpholinocinnamamidine (X) in preference to the addition-elimination to the amidino carbon (Scheme 6).

Consequently, as shown in Scheme 3, the propiolamidine would be activated by the protonation at the amidine nitrogen to form the diaminoallene cation, and readily attacked by a nucleophile, such as hydroxylamine, to give the adduct. The central carbon atom of allene in the adduct corresponds to β-carbon of enamines, so that the prototropic change to the enamino amidine intermediate might take place smoothly. The cyclization process would also be prompted by protonation, and an protonated amino group in the cyclic product would be released to give the amine hydrochloride together with an isoxazole, since the more basic amine, cyclohexylamine, was recovered predominantly in the reaction of *N*-cyclohexyl-*N*′-phenylphenylpropiolamidine (IIi) with hydroxylamine hydrochloride.



Scheme 6.

Experimental

All melting points are uncorrected. The NMR spectra were measured with a Varian A-60 NMR spectrometer, using tetramethylsilane as an internal standard. The mass spectra were obtained using a JEOL-JMS-OIS Mass spectrometer. The IR spectra were determined by means of nujol mulls or liquid films.

Materials. *N,N'*-Dicyclohexylcarbodiimide was obtained commercially, *N,N'*-bis(*p*-methoxyphenyl)carbodiimide was derived from *N,N'*-bis(*p*-methoxyphenyl)chloroformamidiniumchloride,[11] *N,N'*-bis(*p*-nitrophenyl)carbodiimide was synthesized from *p*-nitrophenylisocyanate using 3-methyl-1-phenyl-1-phospha-3-cyclopenten-1-oxide as a catalyst.[12] The other carbodiimides were prepared from the corresponding thioureas employing yellow mercuric oxide.

Preparation of N,N'-*Disubstituted Phenylpropiolamidines (II). Method A: General Procedure*: Metallic sodium (1.15 g, 50 mg-atom) was dispersed in 50 m*l* dry xylene by means of a Sodium Dispersator (Taneda Co., Ltd., Toyama city) at about 110°C in the presence of one drop of oleic acid under dry nitrogen. After cooling to 60°C, triethylamine (5.0 g, 50 mmol) was added, followed by dropwise addition of phenylacetylene (5.2 g, 51 mmol) in 10 m*l* of xylene at a rate so that the reaction temperature was kept at about 60°C. Acetylide formation took place immediately. After the exothermic reaction ceased, the mixture was warmed at the same temperature for 30 min. The corresponding carbodiimide (50 mmol) in 10 m*l* xylene was introduced dropwise at room temperature for 10 min, but no significant change was observed. When dimethylsulfoxide (3.9 g, 50 mmol) in 10 m*l* xylene was added with cooling in a cold water bath, the reaction mixture almost dissolved and turned dark brown.[13] After 30 min, the mixture was poured into ice water, the organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The concentrate was purified by silica gel column chromatography and/or recrystallization.

N,N'-*Dicyclohexylphenylpropiolamidine (IIa).* A yellow viscous oil. IR: 3400 (NH), 2200 (C≡C) cm^{-1}. Further purification on a silica gel column (benzene - ethanol 50 : 1) was not successful. Picrate: mp 187—188°C (decomp., from ethanol). Found: C, 60.55; H, 5.95; N, 12.84%. Calcd for $C_{27}H_{31}N_5O_7$: C, 60.32; H, 5.81; N, 13.03%. IR: 2190 (C≡C) cm^{-1}.

N,N'-*Diphenylphenylpropiolamidine (IIb).* Yellow needles (from *n*-hexane); mp 122—123.5°C. Found: C, 84.89; H, 5.43; N, 9.41%. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45%. IR: 3200 (NH), 2200 (C≡C) cm^{-1}. Picrate: mp 198—200°C (decomp., from methanol). Found: C, 61.52; H, 3.77; N, 13.24%. Calcd for $C_{27}H_{19}N_5O_7$: C, 61.71; H, 3.64; N, 13.33%. IR: 2200 (C≡C) cm^{-1}.

N,N'-*Bis*(p-*tolyl*)*phenylpropiolamidine (IIc).* Yellow needles (from ethanol); mp 140.5—141°C. Found: C, 84.93; H, 6.20; N, 8.58%. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.64%. IR: 3230 (NH), 2220 (C≡C) cm^{-1}. NMR (δ in CCl_4): 2.30 (6H, s, CH_3), 6.85—7.3 (phenyl protons).

N,N'-*Bis*(p-*methoxyphenyl*)*phenylpropiolamidine (IId).* Yellow needles (from ethanol); mp 122—123°C. Found: C, 77.44; H, 5.75; N, 7.82%. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86%. IR: 3350 (NH), 2210 (C≡C) cm^{-1}. NMR (δ in $CDCl_3$): 3.97 (6H, s, OCH_3).

N,N'-*Bis*(p-*chlorophenyl*)*phenylpropiolamidine (IIe).* Colorless needles (from ethanol-*n*-hexane); mp 153—154°C. Found: C, 69.40; H, 3.86; N, 7.50; Cl, 19.41%. Calcd for $C_{21}H_{14}N_2Cl_2$: C, 69.05; H, 3.86; N, 7.67; Cl, 19.41%. IR: 3240, 3160 (NH), 2260 (C≡C) cm^{-1}. NMR (δ in CCl_4): 7.26 (s, phenyl protons).

N,N'-*Dibenzylphenylpropiolamidine (IIg).* Viscous oil. IR: 2200 (C≡C) cm^{-1}. Further purification of this material was not successful, so it was converted into the picrate and characterized. Picrate: mp 190—191°C (decomp., from ethanol). Found: C, 62.71; H, 4.12; N, 12.39%. Calcd for $C_{29}H_{23}N_5O_7$: C, 62.92; H, 4.19; N, 12.65%. IR: 2230 (C≡C) cm^{-1}. NMR (δ in DMSO-d_6): 4.74, 4.88 (4H, benzyl protons).

N,N'-*Dicyclohexyl*-p-*tolylpropiolamidine (IIh).* *p*-Tolylacetylene, instead of phenylacetylene, was converted into sodium acetylide and reacted with *N,N'*-dicyclohexylcarbodiimide in a similar way. A oily crude amidine was crystallized as the benzoate. Benzoate: Colorless crystals (from 50% ethanol); mp 141—142°C. Found: C, 78.08; H, 8.32; N, 6.60%. Calcd for $C_{29}H_{36}N_2O_2$: C, 78.34; H, 8.16; N, 6.30%. IR: 2190 (C≡C) cm^{-1}. NMR (δ in $CDCl_3$): 2.43 (3H, s, CH_3), 3.66 (2H, broad bands, ).

N-*Cyclohexyl*-N'-*phenylphenylpropiolamidine (IIi).* White needles (from *n*-hexane); mp 113—114°C. Found: C, 83.52; H, 7.28; N, 9.14%. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26%. IR: 3190, 3090 (NH), 2190 (C≡C) cm^{-1}. Benzoate: White crystals (from 50% ethanol); mp 115—116°C. Found: C, 79.11; H, 6.57; N, 6.38%. Calcd. for $C_{28}H_{28}N_2O_2$: C, 79.21; H, 6.65; N, 6.60%. IR: 2220 (C≡C) cm^{-1}.

N-n-*Butyl*-N'-*phenylphenylpropiolamidine (IIj).* Yellow needles (from *n*-hexane); mp 55—56°C. Found: C, 82.50; H, 7.31; N, 10.05%. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14%. IR: 3200 (NH), 2200 (C≡C) cm^{-1}. Picrate: mp 169—170°C (decomp., from ethanol). Found: C, 59.24; H, 4.63; N, 13.67%. Calcd for $C_{25}H_{23}N_5O_7$: C, 59.40; H, 4.59; N, 13.86%. IR: 2190 (C≡C) cm^{-1}.

N-*Benzyl*-N'-*phenylphenylpropiolamidine (IIk).* Yellow needles (from *n*-hexane); mp 94—95°C. Found: C, 85.17; H, 5.78; N, 9.18%. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03%. IR: 3200 (NH), 2200 (C≡C) cm^{-1}. NMR (δ in $CDCl_3$): 4.95 (2H, s, CH_2).

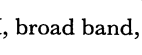
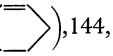
Method B: N,N'-*Bis*(p-*nitrophenyl*)*phenylpropiolamidine (IIf).* Phenylethynylmagnesium bromide was prepared from ethylmagnesium bromide and phenylacetylene in ether in the usual way. One equimolar of *N,N'*-bis(*p*-nitrophenyl)-carbodiimide in tetrahydrofuran and then DMSO (two equimolar) were introduced subsequently at room temperature. The mixture was stirred for 45 min and poured into ice water. After the precipitate was filtered off, the filtrate was extracted with ether. The precipitate and extract were crystallized from ethyl acetate to afford crude amidine. Recrystallization from dimethylformamide gave yellow crystals. Mp 264—265°C (decomp.). Found: C, 65.45; H, 3.88; N, 14.71%. Calcd for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50%. IR: 3350 (NH), 2210 (C≡C) cm^{-1}.

*Syntheses of 5-*N-*Substituted Amino-3-phenylisoxazoles. General Procedure*: A mixture of the phenylpropiolamidine (II) and a slight excess of hydroxylamine hydrochloride in ethanol was refluxed for several hours. After removal of the solvent under reduced pressure, the residue was treated as usual with hot benzene to recover the eliminated amine hydrochloride and the benzene soluble materials were subjected to silica gel column chromatography using a suitable solvent system or purified by recrystallization.

11) H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1237 (1964).

12) T. W. Campbell, J. J. Monagle, and V. S. Fordi, *J. Amer. Chem. Soc.*, **84**, 3673 (1962).

13) In some cases, DMSO was added to the sodium acetylide suspension before addition of a carbodiimide solution. In this case, the sodium phenylacetylide-DMSO complex was observed.[4] However, the order of addition does not seem to affect the yield of amidines.

5-Cyclohexylamino-3-phenylisoxazole (IVa). Colorless needles (from *n*-hexane); mp 128—129.5°C. Found: C, 74.42; H, 7.64; N, 11.78%. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56%. IR: 3370 (NH), 1622, 1501 cm^{-1}. NMR (δ in $CDCl_3$): 5.26 (1H, s, C-4 proton), 4.46 (1H, broad band, NH), 3.25 (1H, broad band, ). Mass (*m/e*): 242 (M^+), 160 (M− ),144, 132, 116, 89, 77.

5-Anilino-3-phenylisoxazole (IVb).[14] Pale yellow plates (from ethanol); mp 136—137°C. Found: C, 76.13; H, 5.28; N, 11.76%. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86%. IR: 3290, 3210 (NH), 1650, 1497, 1473 cm^{-1}. NMR (δ in $CDCl_3$): 5.85 (1H, s, C-4 proton). Mass (*m/e*): 236 (M^+). Aniline hydrochloride, characterized by the IR spectrum, was recovered in 82% yield.

*3-Phenyl-5-*p*-toluidinoisoxazole (IVc).* Colorless crystals (from ethanol); mp 145—146°C. Found: C, 76.67; H, 5.63; N, 11.05%. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19%. IR: 3280, 3200 (NH), 1645, 1510, 1485, 1475 cm^{-1}. NMR (δ in $CDCl_3$): 5.76 (1H, s, C-4 proton), 2.33 (3H, s, CH_3).

*5-*p*-Anisidino-3-phenylisoxazole (IVd).* Colorless needles (from ethanol); mp 150—151°C. Found: C, 72.01; H, 5.24; N, 10.72%. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52%. IR: 3330, 3260 (NH), 1658, 1518, 1502, 1483, 1464 cm^{-1}. NMR (δ in $CDCl_3$): 5.65 (1H, s, C-4 proton), 3.80 (3H, s, OCH_3).

Reaction of IIi with Hydroxylamine hydrochloride. An ethanolic solution of IIi and excess hydroxylamine hydrochloride was refluxed for 5 hr. After removal of the solvent, the concentrate was treated with benzene to separate the released amine hydrochloride, which was characterized by IR spectrum as cyclohexylamine hydrochloride (IR spectrum showed no absorption maximum attributable to the phenyl ring). The soluble material was chromatographed on a silica gel column (benzene - ethanol 50 : 1). The eluted isoxazole was recrystallized from ethanol. Mp 136—137°C. The IR spectrum was identical with that of IVb.

*Synthesis of 5-Anilino-1-*o*-nitrophenyl-3-phenylpyrazole (VIIIe) from β-Morpholinothiocinnamanilide (V).*[10] *β-Morpholinothiocinnamanilide (V):*[15] The reaction of 1-morpholino-1-phenylethylene (9.5 g) with phenylisothiocyanate (6.75 g) in ethyl acetate afforded yellow needles of V (12.8 g, 79%), followed by recrystallization from the same solvent to give an analytically pure sample having mp 154.5—156.5°C (decomp.). Found: C, 70.36; H, 6.31; N, 8.77; S, 9.88%. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63; S, 9.88%. NMR (δ in $CDCl_3$): 5.91 (1H, s, =CH).

Benzoylthioacetanilide (VI):[15] V (9.72 g) in 60 m*l* hot ethanol was treated with 16 m*l* of 2N-HCl and left overnight in a refrigerator. The precipitate was collected and recrystallized from 50% ethanol repeatedly. Yield: 63%. Colorless powder. Mp 78—79.5°C. Found: C, 70.84; H, 5.17; N, 5.59; S, 12.60%. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56%. NMR (δ in $CDCl_3$): 4.62 (s, CH_2), 6.25 (s, =CH), 14.80 (s, enolic OH).

o-Nitrophenylhydrazone of VI (VIIa):[10] To an ethanolic solution of VI (1.72 g), *o*-nitrophenylhydrazine (1.03 g) dissolved in 50% aqueous acetic acid was added and the mixture was heated at 95°C for 5 min. The resulting deposit was filtered off and triturated with ethyl acetate - petroleum ether to give an orange solid (2.1 g, 80%). Recrystallization from ethyl acetate three times afforded orange needles. Mp 169.5—172.5°C (decomp.). Found: C, 64.84; H, 4.70; N, 14.55; S, 8.30%. Calcd for $C_{21}H_{18}N_4O_2S$: C, 64.60; H, 4.65; N, 14.35; S, 8.20%. NMR (δ in acetone-d_6): 4.55 (2H, s, CH_2), 11.05 (1H, broad band, NH).

*5-Anilino-1-*o*-nitrophenyl-3-phenylpyrazole (VIIIe) from VIIa:*[10] VIIa (0.78 g) was cyclized by lead diacetate trihydrate (0.76 g) in a gently refluxing aqueous acetic acid. After 30 min, the mixture was filtered, the filtrate poured into ice water, and the yellow precipitate of VIIIe was collected and washed with water. Yield: 46%. Repeated recrystallization from ethanol afforded yellow needles. Mp 164—165°C. Mixed mp with one derived from IIb; 165—166°C. The respective IR, NMR, and mass spectra of both samples were also superimposable.

*Syntheses of 5-*N*-Substituted amino-3-phenylpyrazoles. 5-Anilino-3-phenylpyrazole (VIIIa):*[9] IIb (1.0 g) reacted with hydrazine dihydrochloride in the presence of an equimolar amount of triethylamine in boiling ethanol for 3 hr. A benzene soluble red oil was triturated with benzene - *n*-hexane to yield a yellow solid, followed by recrystallization from dilute ethanol to give crystalline powders of VIIIa (278 mg, 35%). Mp 153.5—155°C. Found: C, 76.25; H, 5.56; N, 17.60%. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86%. NMR (δ in acetone-d_6): 6.32 (1H, s, C-4 proton).

*General Procedure for Syntheses of 1-Aryl-3-phenyl-5-*N*-substituted Aminopyrazoles.* Phenylpropiolamidine (II) and a slight excess of arylhydrazine hydrochloride were refluxed in ethanol for several hours. After the solvent was distilled off, the residual material was treated with hot benzene in order to recover the eliminated amine hydrochloride. Benzene soluble materials were purified by silica gel column chromatography and/or recrystallization using suitable solvents.

5-Cyclohexylamino-1,3-diphenylpyrazole (VIIIb): Cyclohexylamine hydrochloride (61%) was recovered. After being separated by silica gel column (benzene - ethanol 50 : 1), crude VIIIb was recrystallized from petroleum ether (bp 30—70°C) to afford colorless prisms having mp 67—68.5°C. Yield: 50%. Found: C, 79.75; H, 7.41; N, 13.14%. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24%. NMR (δ in $CDCl_3$): 5.87 (1H, s, C-4 proton).

5-Anilino-1,3-diphenylpyrazole (VIIIc):[10] After separation of aniline hydrochloride [73%, mp 197.5—199°C (decomp.) Lit, mp 198°C. Found: C, 55.36; H, 6.28; N, 10.92; Cl, 27.08%], VIIIc was solidified with *n*-hexane and recrystallization from ethanol to give colorless prisms. Mp 153.5—154.5°C. Found: C, 80.92; H, 5.55; N, 13.55%. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.50%. NMR (δ in $CDCl_3$): 6.46 (1H, s, C-4 proton).

*5-Anilino-3-phenyl-1-*p*-tolylpyrazole (VIIId):* Colorless crystals (from ethanol); mp 141—142.5°C. Found: C, 80.82; H, 5.86; N, 12.66%. Calcd for $C_{22}H_{19}N_3$: C, 81,20; H, 5.89; N, 12.91%. NMR (δ in CCl_4): 6.34 (1H, s, C-4 proton), 2.25 (3H, s, CH_3).

*5-Anilino-1-*o*-nitrophenyl-3-phenylpyrazole (VIIIe):*[10] Yellow needles (from ethanol); mp 165—166°C. Found: C, 70.42; H, 4.65; N, 15.74%. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72%. NMR (δ in acetone-d_6): 6.64 (1H, s, C-4 proton). Mass (*m/e*): 356 (M^+), 310, 207, 102, 77. Aniline hydrochloride was also recovered (73%).

5-Anisidino-1,3-diphenylpyrazole (VIIIf): Colorless prisms (from benzene - *n*-hexane); mp 103—104°C. Found: C, 77.28; H, 5.62; N, 12.41%. Calcd for $C_{22}H_{19}N_3O$: C, 77.39; H, 5.61; N, 12.31%. NMR (δ in $CDCl_3$): 6.30 (1H, s, C-4 proton), 3.76 (3H, s, OCH_3).

14) A. Umani-Ronchi, M. Acampora, G. Gaudiano, and A. Selva, *Chim. Ind.* (Milan), **1967**, 388.

15) S. Hünig, K. Hübner, and E. Benzing, *Chem. Ber.*, **95**, 926 (1962).

5-p-Toluidino-1,3-diphenylpyrazole (VIIIg) and 3-p-Toluidino-1,5-diphenylpyrazole (IXg): After removal of *p*-toluidine hydrochloride (82%), benzene soluble materials were chromatographed on a silica gel column. VIIIg was first eluted with benzene and then IXg with the same solvent. Both were recrystallized from *n*-hexane - benzene to afford analytical samples. VIIIg: Colorless needles. Yield: 40%. Mp 94—95°C. Found: C, 80.95; H, 5.82; N, 13.19%. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91%. NMR (δ in $CDCl_3$): 6.43 (1H, s, C-4 proton), 2.29 (3H, s, CH_3). IXg: Colorless crystals. Yield: 7%. Mp 180—181.5°C. Found: 81.49; H, 6.05; N, 12.88%. NMR (δ in $CDCl_3$): 6.24 (1H, s, C-4 proton), 2.29 (3H, s, CH_3).

5-p-Chloroanilino-1,3-diphenylpyrazole (VIIIh): Colorless prisms (from ethanol); mp 100—101°C. Found: C, 73.25; H, 4.57; N, 12.03; Cl, 10.18%. Calcd for $C_{21}H_{16}N_3Cl$: C, 72.93; H, 4.66; N, 12.15; Cl, 10.25%. NMR (δ in $CDCl_3$): 6.45 (1H, s, C-4 proton).

A Reaction of IIb with Morpholine. A mixture of IIb (7.4 g) and morpholine (2.18 g) in 60 m*l* ethanol was heated for 5.5 hr in the presence of one equivalent of hydrogen chloride. After distilling off the solvent, the residue was suspended in benzene and shaken with aqueous potassium carbonate solution. The resulting benzene solution was washed with water, dried over anhydrous sodium sulfate and concentrated. Recrystallization of the residual solid from ethanol afforded yellow prisms of *N,N'*-diphenyl-*β*-morpholinocinnamamidine (X, 5.0 g, 52%). Mp 137—138°C. Found: C, 78.10; H, 6.58; N, 10.98%. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96%. NMR (δ in $CDCl_3$): 2.80 and 3.64 (8H, CH_2 in morpholine), 5.04 (1H, s, =CH), 6.9—7.5 (phenyl protons).

The authors are grateful to Prof. Makoto Okawara, Tokyo Institute of Technology, for his valuable comments.