Amidrazones and Related Compounds. IV.[1] The Cyclization of Hydrazidines to 2,3,4,5-Tetrahydro-1,2,4,5-tetrazine and 4-Amino-1,2,4-triazole Derivatives

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Three methods of cyclization of hydrazidines are described. The reaction of N^4-arylhydrazidines (**2**) with dimethyl acetylenedicarboxylate in refluxing tetrahydrofuran afforded 6-alkyl and aryl-2-aryl-3-methoxycarbonyl-3-methoxycarbonylmethyl-2,3,4,5-tetrahydro-1,2,4,5-tetrazines (**3**). Oxidation of N^4-aryl-N^2-arylmethylenehydrazidines (**6**) with mercuric oxide in refluxing ethanol gave 3-alkyl and aryl-5-aryl-4-arylamino-1,2,4-triazoles (**7**). 3-Alkyl and aryl-4-arylamino-1,2,4-triazoles (**7f**, **g**) were obtained upon the heating of (**2a**, **e**) in formic acid.

In contrast to amidrazones[2] the use of hydrazidines, nitrogen analogues of amidrazone, as starting materials for the preparation of nitrogen heterocycles has not been extensively studied.

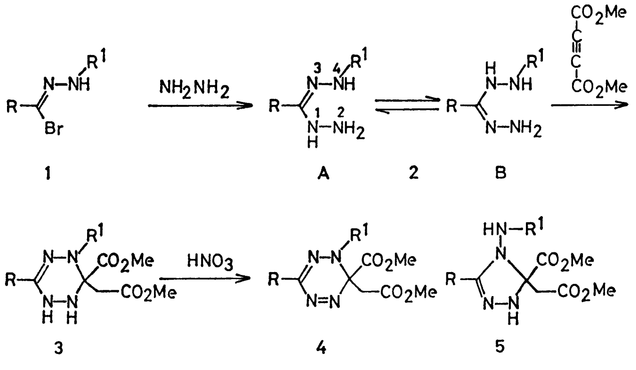
The reaction of N^4-arylhydrazidines with nitrous acid has been reported to give 2,6-diarylpentazines,[3] which were later corrected to be 1-arylamino-5-aryltetrazoles.[4] Methylthiohydrazonium salts have been noted[5] to cyclize in the presence of hydrazines to give 2,5-diphenyltetrazoles through intermediary hydrazidines. The synthesis of 3,5-disubstituted 4-arylamino-1,2,4-triazoles from acylhydrazidines has been investigated by Buzykin and coworkers.[6a,b] Recently, Neunhoeffer *et al.* have prepared some *N*-unsubstituted hydrazidines,[7] and pyrrolo[1,2-*b*][1,2,4,5]tetrazines.[8]

In this paper, the methods of cyclization of hydrazidines to some heterocycles by use of dimethyl acetylenedicarboxylate, mercuric oxide, and formic acid are reported.

Results and Discussion

Hydrazidines (**2**) are available by the reaction of hydrazonyl bromide (**1**) and hydrazine hydrate in alcohol.[9] Although the presence of the tautomerism **2A**$\rightleftharpoons$**2B** of hydrazidine appears possible, no study of it has been reported. However, the formation of 4-amino-1,2,4-triazoles[6,7] and 1-aminotetrazoles[4] supports the tautomerism. All the reported cyclization occured at the N^2 and N^3 positions. However, when **2** were treated with dimethyl acetylenedicarboxylate, compounds cyclized at the N^2 and N^4 positions were formed.

Thus, when N^4-(2-bromo-4-nitrophenyl)benzohydrazide hydrazone (**2a**) was allowed to react with dimethyl acetylenedicarboxylate in refluxing tetrahydrofuran, an orange product was obtained. This compound was proved to be a 1 : 1 adduct on the basis of elemental analysis and its mass spectrum (*m*/*e* 491, M$^+$). The IR spectrum showed NH, C=N, and ester absorptions at 3260, 1625, and 1705 cm^{-1}, respectively. The presence of two methyl and one methylene groups was ascertained by resonance at δ 3.65 (s, 3H), 3.75 (s, 3H), and 3.90 (s, 2H) in the NMR spectrum. However, these data do not distinguish between the tetrahydrotetrazine (**3a**) and dihydrotriazole (**5a**). Therefore, to determine the structure, some reactions were attempted and an oxidized product was obtained upon treatment of the adduct with nitric acid, which was previously used for the oxidation of dihydrotetrazine to tetrazine.[10] The oxidized product showed no NH absorption, but two ester absorptions at 1736 and 1725 cm^{-1}. In the NMR spectrum, the absorptions at δ 3.64, 3.74, and 3.31 were assigned to two methyl and one methylene groups, respectively. The mass spectrum (*m*/*e* 489, M$^+$) and elemental analysis suggest one molar dehydrogenation from the 1 : 1 adduct. From these data, it is concluded that the structure of the adduct is **3a**, 2,3,4,5-tetrahydro-1,2,4,5-tetrazine and the oxidized product is 2,3-dihydro-1,2,4,5-tetrazine (**4**). The physical properties and the spectral data of other tetrazine derivatives are listed in Table 1.



1, 2, 3, 4, 5,	R	R¹
a	C_6H_5	$2\text{-Br-4-NO}_2C_6H_3$
b	4-ClC_6H_4	$2\text{-Br-4-NO}_2C_6H_3$
c	C_6H_5	$4\text{-NO}_2C_6H_4$
d	1-MePr	$2,4\text{-(NO}_2)_2C_6H_3$
e	Me	$2,4\text{-(NO}_2)_2C_6H_3$
f	$4\text{-}i\text{-PrC}_6H_4$	$2\text{-Br-4-NO}_2C_6H_3$

Scheme 1.

The synthesis of nitrogen heterocycles from hydrazidines has also been attempted. Spasov *et al.*[11] have described the oxidation of arylmethylene derivatives of amidrazones with mercuric oxide to yield 3,4,5-triaryl-substituted 1,2,4-triazoles. Then this method was applied to hydrazidines. A mixture of N^2-benzylidene-N^4-(2-bromo-4-nitrophenyl)benzohydrazide hydrazone (**6a**) and mercuric oxide in ethanol was refluxed for 24 h. The elemental analysis, mass spectrum (*m*/*e*

TABLE 1. PHYSICAL PROPERTIES AND SPECTRAL DATA OF **3**

Compound	Yield (%)	Mp (°C) (Solvent)	Molecular formula	Found (Calcd)		IR (KBr) (cm^{-1})			UV (MeOH) (nm, (log ε))
				C%	H%				
3a	77	184—187 (C_6H_5)	$C_{19}H_{18}O_6N_5Br$	46.35 (46.36	3.80 3.68)	3260, 1582,	1705, 1530	1625,	253 (4.21), 423 (4.32)
3b	86	191—193 (THF-MeOH)	$C_{19}H_{17}O_6N_5BrCl$	43.58 (43.32	3.31 3.25)	3260, 1636,	1728, 1582	1702,	238 sh (4.30), 256 sh (4.23), 300 sh (3.99), 403 (4.44)
3c	80	184—186 (C_6H_6)	$C_{19}H_{18}O_6N_5$	55.08 (55.34	4.51 4.40)	3190, 1625,	1735, 1590	1705	227 (4.36), 286 sh (3.96), 405 (4.46)
3d	88	149—151 (MeOH)	$C_{17}H_{22}O_8N_6$	46.36 (46.57	5.04 5.06)	3250, 1655,	2960, 1620	1715,	234 (4.31), 262 (4.19), 398 (4.35)
3e	87	158—160 ($CHCl_3$-MeOH)	$C_{14}H_{16}O_8N_6$	42.21 (42.43	3.93 4.07)	3300, 1712,	3070, 1705,	2960, 1647	228 (4.23), 263 (4.19), 393 (4.28)

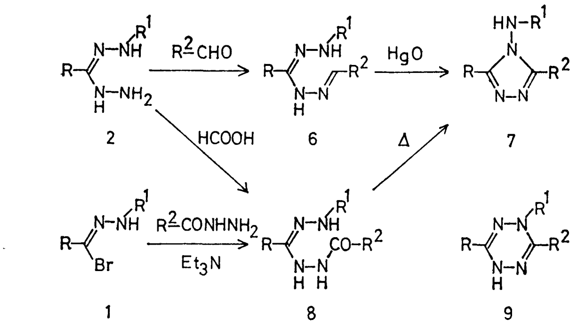
TABLE 2. PHYSICAL PROPERTIES AND SPECTRAL DATA OF **7**

Compound	Yield (%)	Mp (°C) (Solvent)	Molecular formula	Found (Calcd)		IR (KBr) (cm^{-1})			UV (MeOH) (nm, (log ε))
				C%	H%				
7a	48	265—267 a)	$C_{20}H_{14}O_2N_5Br$	55.11 (55.00	3.14 3.20)	3140, 1500,	3060, 1475	1589,	253 (4.36), 326 (4.05)
7b	28	228—231 a)	$C_{22}H_{19}O_2N_6Br$	55.30 (55.12	4.44 4.00)	3130, 1610,	3060, 1580	2900,	220 sh (4.36), 230 sh (4.27), 317 (4.53)
7c	55	244—246 a)	$C_{20}H_{13}O_2N_5BrCl$	51.35 (51.03	3.28 2.78)	3160, 1500,	3080, 1473	1590,	260 (4.41), 324 (4.07)
7d$^{b)}$	29	213—214 (C_6H_6)	$C_{18}H_{18}O_4N_6$	56.32 (56.54	4.83 4.75)	3200, 1618,	3100, 1600,	2960, 1520	242 (4.36), 316 (4.06), 380 sh (3.76)
7e	75	244—245 a)	$C_{26}H_{26}O_2N_5Br$	59.72 (60.00	5.09 5.04)	3170, 1500,	2960, 1488	1593,	264 (4.45), 330 (4.09), 450 sh (2.68)
7f	56	222—224 (MeOH)	$C_{14}H_{10}O_2N_5Br$	46.92 (46.68	3.09 2.78)	3080, 1475,	1580, 1445	1500,	240 (4.29), 326 (4.10), 498 (2.97)
7g	69	260—261 (MeOH)	$C_9H_8O_4N_6$	40.97 (40.91	3.05 3.05)	3120, 1503,	1620, 1415	1600,	220 (4.10), 259 (4.04), 314 (4.11), 445 sh (2.84)

a) C_6H_6-petroleum ether. b) Column chromatographed on silica gel with $CHCl_3$.

435, M$^+$), and IR spectrum (NH absorption at 3140 cm^{-1}) of the product indicate it to be 4-amino-1,2,4-triazole (**7a**) or 2,5-dihydro-1,2,4,5-tetrazine (**9a**). The NMR measurement of a product, whose substituents R and R^2 are the same, would reveal the structure to be symmetric (**7**) or asymmetric (**9**). In the NMR spectrum of products **7e** and **9e** obtained from **6e**, four methyl and two methylidyne groups of the two isopropyl groups on R and R^2 were observed at δ 1.15 (12H, d, J=7.0 Hz) and 2.80 (2H, m, J=7.0 Hz), respectively, and the aromatic protons on R and R^2 were observed at δ 7.01 (4H, d, J=8.2 Hz) and 7.55 (4H, d, J=8.2 Hz). These results show that the product apparently is not asymmetric **9e**, but is symmetric **7e**. The confirmation of the structure of **7** has been further conducted according to reported method,[7] that is, the dehydration of N^2-acyl-N^4-substituted hydrazidines (**8**) to **7**. **8a** prepared from **1a** was heated in acetic acid and the product was identical with **7a**. The physical and spectral data for product **7** from **6a**—**e** are listed in Table 2.

When **2a** was heated in formic acid, a product was obtained. The analytical and mass spectral results suggest **7f** or **9f** to be possible structures. But **7f** is prefered on the basis of the NMR spectrum, which is as follows: six aromatic protons and one NH proton at δ 7.4—7.95 (m) and 9.04 (s), respectively, besides protons due to the 2-bromo-4-nitrophenyl group, which were clearly assigned (see Experimental). The reaction presumably proceeded *via* formylated hydrazidine (**8f**) to **7f**. However, this cyclization method was sometimes



6, 7, 8, 9,	R	R^1	R^2
a	C_6H_5	2-Br-4-$NO_2C_6H_3$	C_6H_5
b	C_6H_5	2-Br-4-$NO_2C_6H_3$	4-$Me_2NC_6H_4$
c	4-ClC_6H_4	2-Br-4-$NO_2C_6H_3$	C_6H_5
d	1-MePr	2, 4-$(NO_2)_2C_6H_3$	C_6H_5
e	4-*i*-PrC_6H_4	2-Br-4-$NO_2C_6H_3$	4-*i*-PrC_6H_4
f	C_6H_5	2-Br-4-$NO_2C_6H_3$	H
g	Me	2, 4-$(NO_2)_2C_6H_3$	H

Scheme 2.

accompanied by by-products and only **7f** and **7g** were obtained in pure forms.

Experimental

All the melting points are uncorrected. The IR, UV, and NMR spectra were measured using a JASCO Model IRA-2 spectrometer, a Shimadzu Model MPS-501 spectrometer, and a Hitachi Model R-20 spectrometer, respectively. A Shimadzu Model UM-3B apparatus was used for the elemental analysis.

Materials. Compounds **1a**,[12] **1b**[12] **1c**,[12] **1d**,[13] **1e**,[13] and **1f**[12] were prepared using reported methods. The hydrazines (**2a**—**f**) were prepared by the method of Hegarty *et al.*[9] The arylmethylene hydrazidines **6a**,[9] **6c**,[9] and **6d**[13] were prepared by known methods. **6b** was prepared by refluxing the EtOH solution of **2a** and *p*-dimethylaminobenzaldehyde for 30 min. Recrystallization from benzene afforded red plates; mp 184—186 °C. Found: C, 55.02; H, 4.11%. Calcd for $C_{22}H_{21}O_2N_6Br$: C, 54.89; H, 4.40%. **6e** was prepared as follows: a mixture of **2f** (1.24 g, 3.2 mmol), *p*-isopropylbenzaldehyde (950 mg, 6.4 mmol), and triethylamine (320 mg, 3.2 mmol) in EtOH (64 ml) was refluxed for 2 h. After cooling, the precipitates were filtered to give **6e** (658 mg, 39% yield). Recrystallization from THF–MeOH gave brown needles; mp 193—195 °C. Found: C, 59.49; H, 5.25%. Calcd for $C_{26}H_{28}O_2N_5Br$: C, 59.77; H, 5.40%.

*2-(2-Bromo-4-nitrophenyl)-3-methoxycarbonyl-3-methoxycarbonylmethyl-6-phenyl-2,3,4,5-tetrahydro-1,2,4,5-tetrazine (**3a**).* A mixture of **2a** (1.0 g, 2.9 mmol) and dimethyl acetylenedicarboxylate (490 mg, 3.4 mmol) in THF (40 ml) was refluxed for 4 h. After evaporation of the solvent under reduced pressure, the residue was washed with a small amount of MeOH and filtered to give **3a** (1.1 g, 77% yield). Recrystallization from benzene afforded orange crystals; mp 184—187 °C. NMR (DMSO-d_6): δ 3.65 (3H, s, $-CH_3$), 3.75 (3H, s, $-CH_3$), 3.90 (2H, s, $-CH_2-$), 7.4—8.3 (8H, m, aromatic H), 10.85 (1H, s, NH), 11.30 (1H, s, NH). MS *m/e* (%): 493 (M^++2, 51), 491 (M^+, 53), 434 (54), 432 (54), 334 (13), 332 (15), 245 (33), 216 (38), 214 (40), 104 (82), 103 (100).

The tetrazines (**3b**—**3e**) were prepared in a manner similar to that described above by refluxing the reaction mixture for 2.5—4 h.

*2-(2-Bromo-4-nitrophenyl)-3-methoxycarbonyl-3-methoxycarbonylmethyl-6-phenyl-2,3-dihydro-1,2,4,5-tetrazine (**4**).* To a suspension of **3a** (500 mg, 1.0 mmol) in AcOH (20 ml) was added nitric acid (0.43 ml) dropwise with cooling and stirring. After the color of the reaction mixture became red, crushed ice was added and the solution was made alkaline with aq sodium carbonate. The resulting precipitates were filtered to give **4** (390 mg, 79% yield). Quick recrystallization from MeOH afforded orange plates; mp 133—136 °C. Found: C, 46.35; H, 3.30%. Calcd for $C_{19}H_{16}O_6N_5Br$: C, 46.54; H, 3.29%. IR (KBr): 3090, 2950, 1736, 1725, 1584 cm^{-1}. UV (MeOH) nm (log ε): 218 (4.46), 231 sh (4.32), 256 sh (4.00), 278 (3.87), 360 (4.32). NMR ($CDCl_3$): δ 3.31 (2H, s, $-CH_2-$), 3.64 (3H, s, $-CH_3$), 3.74 (3H, s, $-CH_3$), 7.3—8.6 (8H, m, aromatic H). MS *m/e* (%): 491 (M^++2, 0.4), 489 (M^+, 0.4), 463 (7.8), 461 (8.0), 404 (5.8), 402 (5.8), 360 (11), 358 (12), 332 (13), 330 (14), 301 (43), 299 (45), 279 (39), 269 (39), 267 (21), 258 (19), 256 (19), 233 (24), 116 (23), 103 (100).

*4-(2-Bromo-4-nitroanilino)-3,6-diphenyl-1,2,4-triazole (**7a**).* A mixture of **6a** (200 mg, 0.41 mmol) and yellow mercuric oxide (260 mg, 1.2 mmol) in EtOH (120 ml) was refluxed for 24 h. After the inorganic materials were filtered off, the filtrate was concentrated under reduced pressure and the resulting precipitates were filtered to give **7a** (138 mg, 48% yield). Recrystallization from benzene–petroleum ether afforded a pale yellow powder; mp 265—267 °C. MS *m/e* (%): 437 (M^++2, 41), 435 (M^+, 43), 221 (43), 192 (51), 118 (36), 103 (58), 89 (100). The triazoles (**7b**—**e**) were prepared in a manner similar to that described above by refluxing the reaction mixture for 15—28 h. The NMR spectrum of **7e** ($CDCl_3$): δ 1.15 (12H, d, J=7.0 Hz, $-CH_3$ on isopropyl), 2.80 (2H, m, J=7.0 Hz, CH on isopropyl), 5.98 (1H, d, J=9.0 Hz, 6-H on R^1), 7.01 (4H, d, J=8.2 Hz, *o*- or *m*-H on R and R$_2$), 7.55 (4H, d, J=8.2 Hz, *o*- or *m*-H on R and R^2), 7.73 (1H, dd, J=9.0 and 2.2 Hz, 5-H on R^1), 8.21 (1H, d, J=2.2 Hz, 3-H on R^1), 8.80 (1H, s, NH).

*N^4-(2-Bromo-4-nitrophenyl)-N^2-benzoylbenzohydrazide hydrazone (**8a**).* To a solution of **1a** (600 mg, 1.5 mmol) and benzoylhydrazine (245 mg, 1.8 mmol) in THF (10 ml) was added a solution of triethylamine (300 mg, 3.0 mmol) in THF (3 ml) dropwise with stirring at room temperature. After stirring for an additional 2 h, the resulting precipitates were removed by filtration and the filtrate was evaporated under reduced pressure giving an oily residue. To the residue was added a small amount of MeOH to lead to solidification. The solids were collected by filtration and recrystallized once from MeOH–THF to give **8a** (303 mg, 44% yield). An additional recrystallization afforded orange needles; mp 196—198 °C. Found: C, 53.16; H, 3.39%. Calcd for $C_{20}H_{16}O_3N_5Br$: C, 52.87; H, 3.55%. IR (KBr): 3440, 3280, 1653, 1588, 1508, 1488 cm^{-1}.

*Cyclization of **8a** to **7a**.* A solution of **8a** (100 mg, 0.22 mmol) in AcOH (3.0 ml) was refluxed for 30 min. After removal of the solvent under reduced pressure, the residual solid was washed with a small amount of MeOH and collected by filtration. One recrystallization from MeOH afforded white needles; mp 265—267 °C (60 mg, 62% yield). The mp and IR spectrum were identical to those of **7a**.

*4-(2-Bromo-4-nitroanilino)-3-phenyl-1,2,4-triazole (**7f**).* A solution of **2a** (200 mg, 0.57 mmol) in formic acid (1.0 ml) was refluxed for 2 h. After cooling, a small amount of MeOH was added to the reaction mixture to give crystalline precipitates, which were collected by filtration and recrystallized once from MeOH to give **7f** (116 mg, 56% yield). MS *m/e* (%): 361 (M^++2, 84), 359 (M^+, 86), 145 (36), 104 (100). NMR (DMSO-d_6): δ 6.28 (1H, d, J=9.0 Hz, 6-H on R^1), 7.4—7.95 (6H, m, aromatic H on R and the triazole ring), 8.08 (1H, dd, J=9.0 and 2.2 Hz, 5-H on R^1), 8.45 (1H, d, J=2.2 Hz, 3-H on R^1), 9.04 (1H, s, NH).

*4-(2,4-Dinitroanilino)-3-methyl-1,2,4-triazole (**7g**).* A solution of **2e** (300 mg, 1.2 mmol) in formic acid (3.0 ml) was refluxed for 1 h. Water was added to the reaction mixture and the solution was allowed to stand overnight. The resulting precipitates were collected by filtration to give **7a** (216 mg, 69% yield).

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