Mono-*N*-amino Salts of Benzodiazines and Naphthyridines

Yasumitsu Tamura, Yasuyoshi Miki, Jun-ichi Minamikawa, and Masazumi Ikeda

Faculty of Pharmaceutical Sciences, Osaka University,
Toneyama, Toyonaka, Osaka, Japan

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The mono-*N*-amino salts of 3-phenylcinnoline, phthalazine, 1-phenylphthalazine, 4-phenylquinazoline, 2-phenylquinoxaline, 1,5- and 1,8-naphthyridines are in high yields prepared by direct *N*-amination of the parent heterocycles with *O*-mesitylenesulfonylhydroxylamine. With the one expection of 3-phenylcinnoline, the site of *N*-amination was determined by mass and nmr spectral techniques. The results indicate that the *N*-amination occurs preferentially at the least sterically hindered nitrogen atom.

Heteroaromatic *N*-imines have recently received increasing attention as synthetic intermediates in heterocyclic chemistry (1). In a series of previous papers we have shown that *O*-mesitylenesulfonylhydroxylamine (MSH) (2) reacts with a variety of heteroaromatic tertiary amines including pyridines (3), bipyridyls (4), quinolines (3a, 5), isoquinolines (3a, 5), benzo[*h*]quinoline (3a, 6), benzo[*f*]quinoline (3a, 6), and azoles (7) to give the corresponding *N*-amino salts which produce unisolable *N*-imine intermediates upon base treatment. This method was found to have many advantages over the other known methods (8); (i) the scope is wide, (ii) the yields are high, (iii) the procedure is very simple, and (iv) the reaction conditions are extremely mild.

We now report further application of this method to the syntheses of mono-*N*-amino salts of benzodiazines and some naphthyridines (9).

Syntheses of the mono-*N*-amino salts of 3-phenylcinnoline (I), phthalazine (II), 1-phenylphthalazine (III), 4-phenylquinazoline (IV), 2-phenylquinoxaline (V), 1,5- (VI) and 1,8-naphthyridine (VII) were readily accomplished by utilizing a previously described procedure (3). Thus, the parent heterocycles (I-VII) were treated with an equimolar amount of MSH in methylene chloride under ice-cooling for 10 minutes to give the corresponding crystalline mono-*N*-amino mesitylenesulfonates in good to high yields (Table I). Attempts to prepare the di-*N*-amino salts were unsuccessful.

To confirm the structures of these *N*-amino salts they were converted into the *N*-benzoylimino derivatives, whose structures should be readily ascertained by an examination of the spectral properties. Benzoylation of the *N*-amino salts was effected simply by heating at 90-95° with benzoyl chloride (Table II) (10).

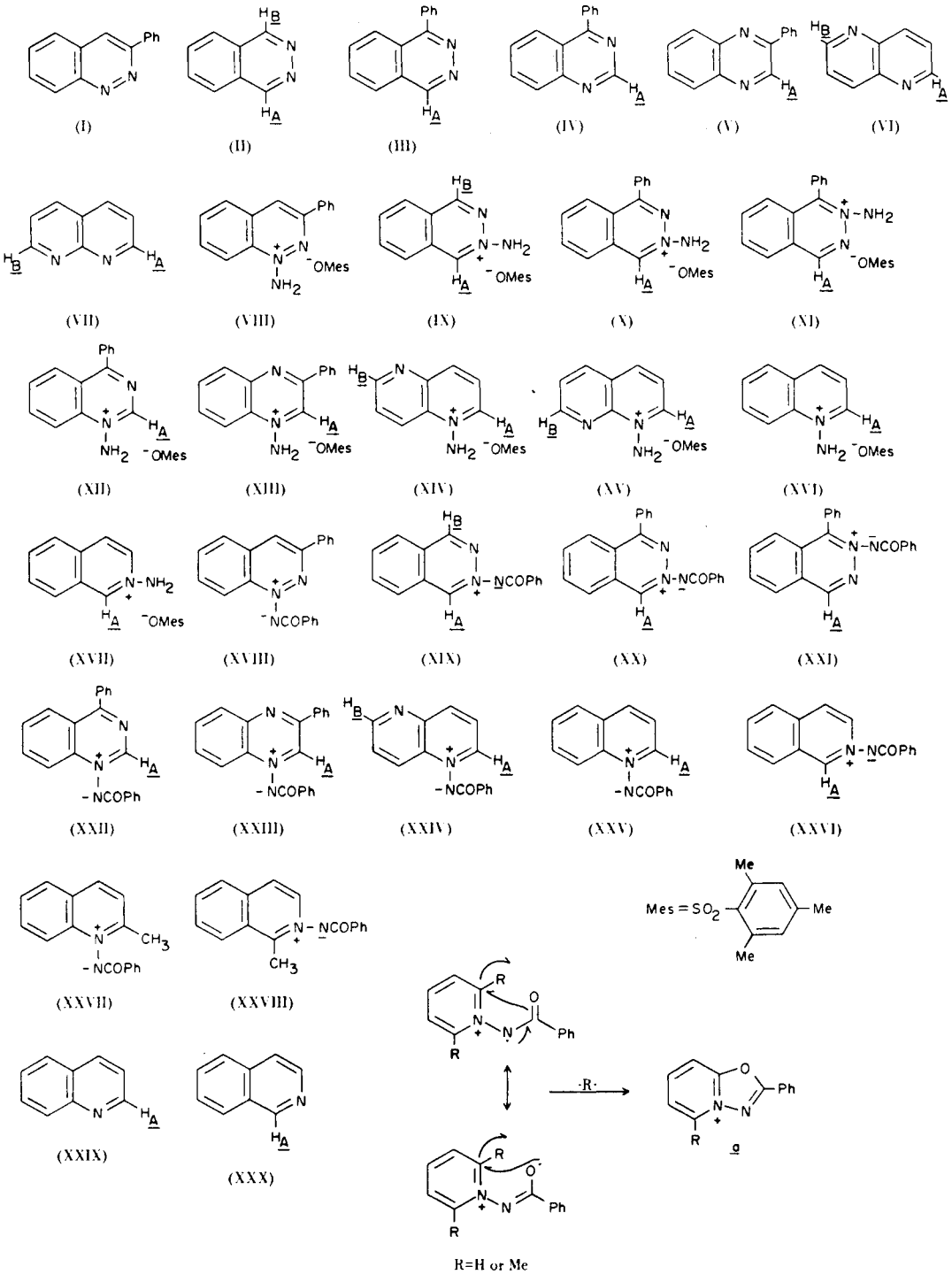
The ir spectra (in potassium chloride) of the *N*-benzoylimines (XVIII-XXIV) showed three strong bands at 1590-1595, 1545-1565, and 1310-1330 cm^{-1}, which are in good agreement with reported values for *N*-benzoylimino-

TABLE I

Preparation of *N*-Amino Salts of Benzodiazines and Naphthyridines

Compd.	M.p. °C	Yield %	Formula	Calcd. % C	H	N	Found % C	H	N
VIII	186-188 (a)	65	$C_{23}H_{23}N_3O_3S$	65.54	5.50	9.97	65.64	5.48	9.80
IX	157-158	53	$C_{17}H_{19}N_3O_3S$	59.12	5.55	12.17	58.83	5.46	12.12
X	144-145 (a,b)	60 (c)	$C_{23}H_{23}N_3O_3S$	65.54	5.50	9.97	65.66	5.58	9.96
XII	166-167 (a)	51	$C_{23}H_{23}N_3O_3S$	65.54	5.50	9.97	65.30	5.52	9.91
XIII	218 (a)	94	$C_{23}H_{23}N_3O_3S$	65.54	5.50	9.97	65.76	5.60	10.19
XIV	190	81	$C_{17}H_{19}N_3O_3S$	59.12	5.55	12.17	59.13	5.58	12.02
XV	128-129	72	$C_{17}H_{19}N_3O_3S$	59.12	5.55	12.17	59.00	5.63	11.92

(a) Homogeneity was checked by nmr spectra. (b) Obtained after several recrystallizations from methanol-ethyl acetate. (c) This yield contains the minor product (XI) (*ca.* 10%).



pyridinium, quinolinium, and isoquinolinium betaines (5, 8). The absence of carbonyl absorption bands above 1600 cm^{-1} suggusts that they have betaine-like structures $=\overset{+}{N}\text{-}N=\overset{O^-}{\overset{|}{C}}\text{-}Ph$ with highly polarized carbonyl groups. No correlation could be found between the positions of the longest absorption maxima and the structures of the betaines. For examples, XIX-XXI, XXV, and XXVI are white to pale yellow crystals and have the longest absorption maximum at 380-400 nm, while XVIII and XXII are colored deep yellow and show a bathochromic shift of the maximum to 430-450 nm. The positions of the absorption

TABLE II

Preparation of *N*-Benzoylimino Betaines of Benzodiazines and Naphthyridines

Compd.	M.p. °C	Yield %	Formula	Calcd. % C	H	N	Found % C	H	N
XVIII	226-228	75	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	77.31	4.58	12.93
XIX	203-204	86	$C_{15}H_{11}N_3O$	72.27	4.45	16.86	72.03	4.52	16.84
XX	204-206	40 (a)	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	77.74	4.75	12.86
XXI	245-246	8 (a)	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	77.48	4.59	12.74
XXII	223-224	62	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	77.60	4.67	12.69
XXIII	192	66	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	77.74	4.78	12.94
XXIV	153-155	60	$C_{15}H_{11}N_3O$	72.27	4.45	16.86	71.97	4.50	16.41

(a) Overall yield from III.

TABLE III

Spectral Data of *N*-Benzoylimino Betaines

Compd.	UV, nm (log ε) dioxane	ethanol	Mass m/e(rel. intensity %)
XVIII	258 (4.55) 299 sh (4.07) 358 (4.62) 448 (4.07)	259 309 sh 421	325 (7) 206 (29) 105 (100)
XIX	256 (4.21) 282 sh (4.03) 342 sh (4.14) 383 (4.30)	285 304 357	249 (11) (a) 248 (11) 130 (59)
XX	252 (4.23) 285 (4.10) 349 sh (4.10) 384 (4.21)	240 296 356	325 (4) (a) 324 (4) 206 (10)
XXI	277 sh (4.13) 342 (3.76) 401 (3.68)	237 286 304 sh 357	325 (56) (a) 206 (4)
XXII	259 (4.11) 340 (3.84) 370 (3.84) 435 (3.90)	231 349	325 (6) (a) 324 (9) 206 (18)
XXIII	254 (4.44) 289 (4.30) 364 sh (4.13) 390 (4.23) 407 sh (4.20)	254 287 385 402 sh	325 (40) 324 (37) 206 (100)
XXIV	265 (4.15) 321 (3.51) 370 sh (3.67) 412 (3.79)	250 312 318 375	249 (26) 248 (57) 130 (100)
XXV (5)	260 sh (4.22) 319 (3.70) 355 (3.82) 402 (3.91)	234 320	248 (47) 247 (100) 129 (72)

TABLE III (Continued)

Compd.	UV, nm (log ε) dioxane	ethanol	Mass m/e(rel. intensity %)
XXVI (5)	278 (4.03) 289 (4.05) 327 sh (3.95) 349 sh (4.00) 381 (4.11)	238 280 sh 334	248 (75) 247 (100) 129 (53)
XXVII (5)	284 sh (3.95) 323 (3.90) 334 (3.92) 362 (3.85)	238 321	262 (4) 247 (55) 143 (100)
XXVIII (5)	298 sh (3.60) 314 (3.67) 322 (3.71) 331 (3.58) 368 (3.27)	231 320	262 (4) 247 (54) 143 (100)

(a) The base peak is an ion at m/e 77.

maxima are also dependent upon the solvent employed; thus a blue shift of 20-50 nm has been observed in changing the solvent from dioxane to alcohol.

Since the two nitrogen atoms of phthalazine (II), 1,5- (VI), and 1,8-naphthyridines (VII) are equivalent, the site of *N*-amination is unequivocal. However, *N*-amination of 3-phenylcinnoline (I), 1-phenylphthalazine (III), 4-phenylquinazoline (IV), and 2-phenylquinoxaline (V), in which the two nitrogen atoms are non-equivalent, is capable of yielding two possible isomers. Indeed, benzoylation of a crude product from the reaction of III and MSH gave two isomeric *N*-benzoylimines XX and XXI in a ratio of *ca.* 5:1. Only one of the two *N*-amino salts (X and XI) could be isolated as a pure compound by several recrystallizations and was assigned X. In contrast, similar treatment of I, IV and V gave only one of the possible *N*-benzoylimines, XVIII, XXII and XXIII, respectively.

The establishment of the site of *N*-amination in the unsymmetrically substituted phthalazine (III) and quinoxaline (V), and 4-phenylquinazoline (IV) was made by the following two methods; (i) the mass spectrometry of the *N*-benzoylimines, and (ii) a comparison of the nmr spectra of the mono-*N*-amino salts or *N*-benzoylimines with those of the parent heterocycles.

We have already shown that one of the most characteristic mass spectral fragmentation of the *N*-benzoylimines of pyridine and 2,6- lutidine is loss of hydrogen (at the 2-position) and a methyl radical, respectively, from the molecular ion to give an ion represented by the fully aromatic structure *a* (11, 12). The origin of the eliminating hydrogen has been established by deuterium labeling experiments (11). The same trend has been observed in the mass spectra of the quinoline (XXV, XXVII) and isoquinoline (XXVI, XXVIII) series (5, 11). In particular, the mass spectra of XXVII and XXVIII do not show an $[M-1]^+$ ion peak due to the presence of a methyl substituent at the position which the cyclization takes place, but give an intense $[M-CH_3]^+$ ion peak. In the present study it was confirmed that the mass spectra of the *N*-benzoylimines XIX and XXIV also show characteristic $[M-1]^+$ ion peaks (Table III). Consequently, this information can be used to assign the site of *N*-amination. The mass spectrum of XX shows an expected $[M-1]^+$ ion peak, while the isomeric XXI gives no $[M-1]^+$ ion peak and, instead, an intense $[M-C_6H_5]^+$ ion peak (13), as anticipated. *N*-Benzoylimines XXII and XXIII also show an $[M-1]^+$ ion peak as expected from the assigned structures.

An alternative method to determine the site of *N*-amination is an application of nmr spectroscopy. It can be seen from Table IV that the conversion of the heterocycles into the *N*-amino salts or *N*-benzoylimines produce considerable shielding of H-2 (H_A) in quinoline, 1,5- and 1,8-naphthyridines and H-1 (H_A) in isoquinoline and phthalazine. This is also evident from comparison of the chemical shifts of H_A and H_B in IX, XIV, XV, XIX, and XXIV. This shift is attributed to the proximate presence of a quarternary nitrogen atom. Hence a comparison of the chemical shift of H-2 (H_A) in the *N*-amino salts or *N*-benzoylimines of the quinoline-type compounds and H-1 (H_A) in those of the isoquinoline-type compounds with those of the parent heterocycles should provide a very useful aid in the structural assignment of the *N*-aminated products. For examples, the H_A signal of XX is shifted 1.25 ppm to lower filed than that of III, while the H_A signal of the isomeric XXI remains almost unchanged. In the nmr spectra of *N*-amino salt XII and *N*-benzoylimine XXII, H_A signals are shifted 0.59 and 0.30 ppm to lower fields than that of IV, This finding closely parallels the results reported for orientation of *N*-oxide formation with peracid (14). On the basis of this conclusion, the structures of *N*-amino salt and *N*-benzoylimine of 3-phenylcinnoline (I) were tentatively

TABLE IV

Nmr Spectra (in τ values) of the *N*-Amino Salts and *N*-Benzoylimino Betaines

Compd.	Solvent (a)	H_A (b)	H_B (b)	Compd.	Solvent (a)	H_A (b)	H_B (b)
IX	A	0.25	0.48	XIV	B	0.49	0.63
XIX	C	-1.00	0.61	XXIV	C	0.55	0.80-1.00 (c)
II	A	0.82	0.82	VI	B	0.91	0.91
	C	0.34	0.34		C	1.03	1.03
X	B	-0.18	-	XV	B	0.51	0.62
XX	C	-0.84	-	VII	B	0.84	0.84
XXI	C	0.37	-	XVI (5)	B	0.54	-
III	B	0.10	-	XXV (5)	C	0.68	-
	C	0.41	-	XXIX	B	0.88	-
XII	B	0.03	-		C	1.19	-
XXII	C	0.23	-	XVII (5)	B	0.12	-
IV	B	0.62	-	XXVI (5)	C	0.06	-
	C	0.53	-	XXX	B	0.48	-
XIII	B	0.04	-		C	0.87	-
XXIII	C	-0.89	-				
V	B	0.35	-				
	C	0.74	-				

(a) Using (A) deuterium oxide and (B) deuteriodimethylsulfoxide with 3-(trimethylsilyl)propanesulfonic acid sodium salt, and (C) deuteriochloroform with tetramethylsilane, as internal references. (b) Chemical shifts of H-6 and H-8 are nearly identical. (c) H_A and H_B refer to the protons indicated in the formula.

assigned VIII and XVIII, respectively.

Further studies on the chemistry of these *N*-amino salts are in progress.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Hitachi EPI G-2 spectrophotometer, uv spectra on a Hitachi 124 spectrophotometer, nmr spectra on a Hitachi R-20A spectrometer and mass spectra on a Hitachi RMU-6D mass spectrometer operating at 70 eV.

Materials.

Phthalazine (II) was obtained commercially. 3-Phenylcinnoline (I) (15), 1-phenylphthalazine (III) (16), 4-phenylquinazoline (IV) (17), 2-phenylquinoxaline (V) (18), 1,5- (VI) (19), and 1,8-naphthyridine (VII) (20) were synthesized as described in the literature.

General Procedure for *N*-Amination.

To an ice-cooled solution of a benzodiazine or naphthyridine (1 mmole) in methylene chloride (2 ml.) was added dropwise a solution of MSH (1 mmole) in methylene chloride (2 ml.). The reaction mixture was allowed to stand at room temperature for 10 minutes. After addition of ether, the precipitated crystals were collected and recrystallized from methanol-ethyl acetate to give crystals of a mono-*N*-amino mesitylenesulfonate. For the elemental analyses, yields, and melting points, see Table I.

General Procedure for *N*-Benzoylation.

A mixture of an *N*-amino salt and a large excess of benzoyl chloride was heated at 90-95° for 2-3 hours. The excess benzoyl chloride was evaporated under reduced pressure and the residue was washed with ether, made alkaline with 10% potassium hydroxide solution and extracted with chloroform. The dired extract was concentrated to give crystals of an *N*-benzoylimino betaine, which was recrystallized from benzene. The *N*-benzoylimines XX and XXI were separated by preparative tlc (Alumina PF_{254}) using benzene-ethyl acetate (1:2) as solvent. For the elemental analyses, yields, and melting points, see Table II.

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