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Heterocycles. IV.[1] Reactions of 2-Amino-3*H*-1,4-benzodiazepines with Primary Amines and Hydroxylamines

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Substitution of the amino group of 2-amino-3*H*-1,4-benzodiazepines such as **1** and **2** with primary amines and hydroxylamines was investigated and the 2-substituted compounds **3**—**19**, **21** and **37** were synthesized as shown in Table I. In the case of the reaction with hydroxylamine, however, a 2-aminomethylquinazoline 3-oxide (**20**) was obtained from a 2-amino- and a 2-methylamino-benzodiazepines (**1** and **3**) in addition to 2-hydroxyamino-1,4-benzodiazepine (**21**). This data show that ring opening at the N-4: C-5 double bond occurred. A similar ring opening in a 2-methylamino-1,4-benzodiazepine 4-oxide (**4**) furnished a quinazoline-2-carboxaldehyde oxime 3-oxide (**40**). The derivatives of **21** and its oxide (**37**) were prepared as exemplified by the synthesis of oxadiazolo[4,3-*a*][1,4]-benzodiazepines (**25** and **39**).

In a previous paper,[3] we reported a new method for the synthesis of 2-amino-3*H*-1,4-benzodiazepine derivatives and their facile conversion with acid in methanol to 1,4-benzodiazepin-2-ones. This high reactivity of the amidine part of the 2-aminobenzodiazepines prompted us to investigate nucleophilic substitution[4] at the 2-position. We now report reactions of certain 2-amino-1,4-benzodiazepines with certain primary amines and hydroxylamines.

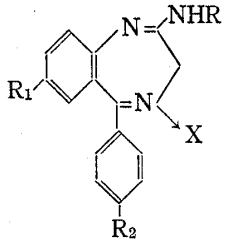
First we tried substitution with primary amines and found that the 2-amino group was easily converted into the corresponding substituted-amino groups in the presence of an acid catalyst. Thus when 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**1**)[3] was heated with methylamine hydrochloride in ethanol, the 2-methylamino derivative (**3**) was obtained in 86% yield. Under similar conditions, the 4N-oxide (**2**)[5] afforded **4**. Compounds **3** and **4** were identified by comparison of their infrared (IR) spectra with those of authentic samples prepared by the known method.[5,6] This reaction (**1** or **2**→**3** or **4**) was applicable to other 2-amino-1,4-benzodiazepines to afford compounds **5**—**13** (Table I).

Similarly, when **1** and **2** were treated with O-methyl- or O-benzyl-hydroxylamine, 2-alkoxyamino derivatives such as **14**, **15** and **16** were obtained. Other compounds **17**—**19** were also prepared (Table I) by this procedure.

Reaction of **1** with hydroxylamine hydrochloride, on the other hand, resulted in the formation of two isomeric products (**20** and **21**). The ratio of **20** and **21** varied with the reaction conditions. At higher reaction temperatures **20** was obtained as the major product (74%) whereas at lower temperatures (0—10°) compound **21** predominated (70%).

1) Part III: K. Meguro and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1263 (1973).
2) Location: *Juso, Higashiyodogawa-ku, Osaka, Japan.*
3) Part II of this Series: K. Meguro, H. Tawada, and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1253 (1973).
4) Similar substitution reactions of amidines are known, especially in the open-chain systems: See, for example, P.A.S. Smith, "Open-chain Nitrogen Compounds," Vol. 1, W.A. Benjamin, Inc., New York, 1965, p. 180.
5) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).
6) L.H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

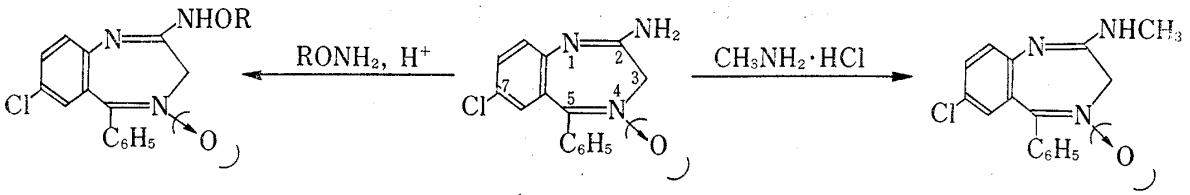
TABLE I. 2-Substituted-1,4-benzodiazepines



Compd. No.	R_1	R_2	X	R	Recrystn.[a] from	mp (°C)[b]	Method[c]
3	Cl	H		Me	Ac	240—241[d]	A
4	Cl	H	O	Me	EtOH	235—236[e]	A
5	H	H		*n*-Bu	Eth-IPE	130—131	A
6	Cl	H		$(CH_2)_2OH$	Eth	172—173	B
7	Cl	H		$(CH_2)_3OH$	AcOEt	203—205	B
8	Cl	H		$(CH_2)_2NEt_2$	THF-Eth	203—204[f]	B
9	Cl	H		$(CH_2)_3NMe_2$	IPE	159—160	B
10	Cl	H		CH_2COOEt	IPE	97— 98	C
11	Cl	H			IPE	150—151	B
12	NO_2	H		$(CH_2)_3NMe_2$	MeOH	130—132	B
13	NO_2	H		CH_2COOEt	Ac-H	194—195	C
14	Cl	H		$OCH_2C_6H_5$	MeOH	180—182	D
15	Cl	H	O	OCH_3	MeOH	229—231	E
16	Cl	H	O	$OCH_2C_6H_5$	MeOH	220—222	D
17	Cl	OCH_3		OCH_3	B	192—194	E
18	H	H		$OCH_2C_6H_5$	MeOH	179—180	D
19	NO_2	H		$OCH_2C_6H_5$	MeOH	215—216	F
21	Cl	H		OH	Eth-H	136—138[h]	G
37	Cl	H	O	OH	Dic-H	236—237 (d.)	H

Compd. No.	Yield, %	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3	86	$C_{16}H_{14}N_3Cl$						
4	94	$C_{16}H_{14}ON_3Cl$						
5	61	$C_{19}H_{21}N_3$	78.31	7.26	14.42	78.63	7.31	14.49
6	87	$C_{17}H_{16}ON_3Cl$	65.07	5.14	13.39	65.15	5.02	13.60
7	91	$C_{18}H_{18}ON_3Cl$	65.95	5.53	12.82	65.85	5.59	12.91
8	55	$C_{21}H_{25}N_4Cl \cdot 2(C_6H_3O_7N_3)$	47.92	3.78	16.94	48.22	3.69	16.95
9	81	$C_{20}H_{23}N_4Cl$	67.69	6.53	15.79	67.22	6.23	15.57
10	62	$C_{19}H_{18}O_2N_3Cl$	64.13	5.10	11.81	64.43	5.40	11.25
11	80	$C_{20}H_{16}ON_3Cl$	68.86	4.33	12.05	68.47	4.48	11.96
12	82	$C_{20}H_{23}O_2N_5$	65.73	6.34	19.17	65.21	6.27	19.13
13	78	$C_{19}H_{18}O_4N_4$	62.28	4.95	15.29	62.36	4.96	14.99
14	72	$C_{22}H_{18}ON_3Cl$	70.30	4.83	11.18	70.52	4.86	11.16
15	79	$C_{16}H_{14}O_2N_3Cl$	60.86	4.47	13.31	60.96	4.34	13.45
16	71	$C_{22}H_{18}O_2N_3Cl$	67.43	4.63	10.72	67.47	4.63	10.69
17	35[g]	$C_{17}H_{16}O_2N_3Cl$	61.91	4.89	12.74	61.98	4.72	12.47
18	65[g]	$C_{22}H_{19}ON_3$	77.39	5.61	12.31	77.44	5.57	12.29
19	25[g]	$C_{22}H_{18}O_3N_4$	68.38	4.70	14.50	68.35	4.55	14.50
21	70	$C_{15}H_{12}ON_3Cl$						
37	71.5	$C_{15}H_{12}O_2N_3Cl$	59.71	4.01	13.93	59.59	3.88	13.95

a) Ac: acetone, Eth: ethyl ether, THF: tetrahydrofuran, IPE: isopropyl ether, H: *n*-hexane, B: benzene, Dic: dichloromethane. *b*) uncorrected *c*) See Experimental Section. *d*) lit.[5] mp 240—241°. *e*) lit.[5] mp 236—236.5°. *f*) dipicrate *g*) This was the result from a single experiment and no attempts were made to obtain optimum yields. *h*) powdery compound (lit.[5] mp 126—130°) Mass Spectrum: *m/e* 285 (M^+).



14 : R=$CH_2C_6H_5$
15 : R=CH_3, 4-oxide
16 : R=$CH_2C_6H_5$, 4-oxide

1
2 : 4-oxide

3
4 : 4-oxide

Chart 1

Compound **20**, which analyzed for $C_{15}H_{12}ON_3Cl$, gave a positive ninhydrin test and showed IR absorption bands at 3350 and 3290 cm^{-1} indicating the presence of a primary amino group. Acetylation of **20** afforded an N-acetate (**22**) which showed an amide carbonyl band at 1650 cm^{-1}. The quinazoline oxide structure was finally assigned to **20** from its ultraviolet (UV) absorption spectrum which is very similar to those of known quinazoline oxides, *e.g.*, 6-chloro-2-chlormethyl-4-phenylquinazoline 3-oxide.[7]

Compound **21**[8] was obtained as a powder and its molecular formula is the same as **20** as shown by its mass spectrum (M^+=285). Compound **21** gave a positive ferric chloride test suggesting the presence of an amidoxime structure and formed an O-acetate (**23**) on acetylation. This acetate (**23**) exhibited a band at 1750 cm^{-1} attributable to an acetoxy group. Catalytic hydrogenation of **21** over Raney nickel regenerated **1**, while reduction with zinc in acetic acid gave a dihydro compound (**24**). Compound **24** was identical with the sample synthesized from a 2-amino-4,5-dihydro-1,4-benzodiazepine (**26**) which was prepared by reduction of **1** with lithium aluminium hydride. A tricyclic compound, an oxadiazolo-[4,3-*a*][1,4]benzodiazepine (**25**)[8] was synthesized from **21** by the reaction with N,N'-carbonyl-bis(2-methylimidazole). Compound **25** showed a carbonyl band at 1775 cm^{-1}. These chemical transformations clearly support structure **21**.

The formation of **20** probably arises from cleavage of the N-4: C-5 double bond of **21** to form intermediate **28**, because **21** gave **20** on heating with hydroxylamine. However, the formation of **20** from **1** *via* intermediate **29** by ring opening at N-4: C-5 of **1** cannot be excluded.

The substitution with hydroxylamine occurred with the 2-methylamino derivative (**3**). In this case, however, the quinazoline **20** was obtained as the major product (81%) whereas **21** was obtained only in poor yield (5%), even when the reaction was performed at room temperature. This showed that in compound **3** the ring opening to form **30** occurred preferably to the substitution to form **21** because of the decreased susceptibility of C-2 to nucleophilic attack.

The preferential ring opening in **3** as versus substitution is consistent with the following data: In the 4,5-dihydro-diazepine (**27**) which lacks the N-4: C-5 double bond, treatment with hydroxylamine afforded **24** in good yield. On the other hand, when a 2,3-dihydro-1*H*-1,4-benzodiazepine (**31**)[9] or 1,4-benzodiazepin-2-ones (**32** and **33**)[10] were treated with hydroxylamine hydrochloride in ethanol, the corresponding ring-opened compounds **34**, **35**[11] and **36**[11] were obtained.

7) L.H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).
8) This compound has recently been reported by J.B. Hester, Jr., D.J. Duchamp and C.G. Chidester, *Tetrahedron Letters*, **1971**, 1609.
9) L.H. Sternbach, E. Reeder, and A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).
10) L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
11) During the course of our investigation, the synthesis of hydrates of a 2-hydroxyimino-1,4-benzodiazepine (**21**) and its N^1-methyl analog by the same reaction was reported by Yamamoto, *et al.* (Japanese Patent Publication 20911 (1970)). Although the melting point reported by them as **21** hydrate was somewhat different from that of **35** prepared by us (see Experimental), both of their compounds seem to be the same as **35** and **36**.

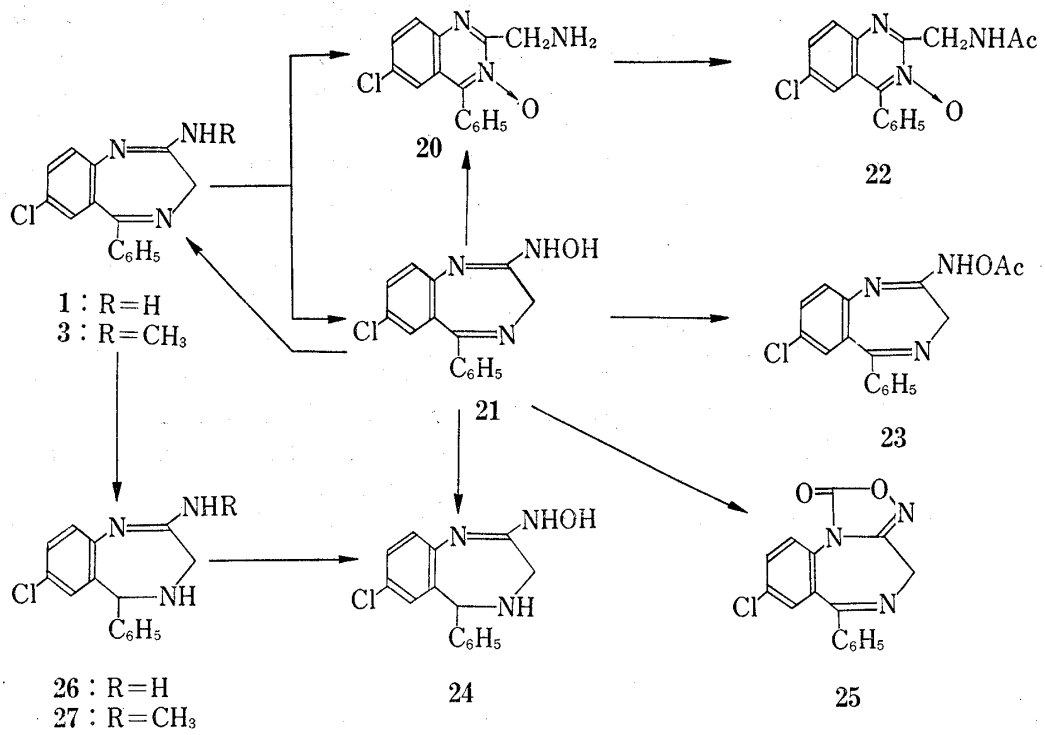


Chart 2

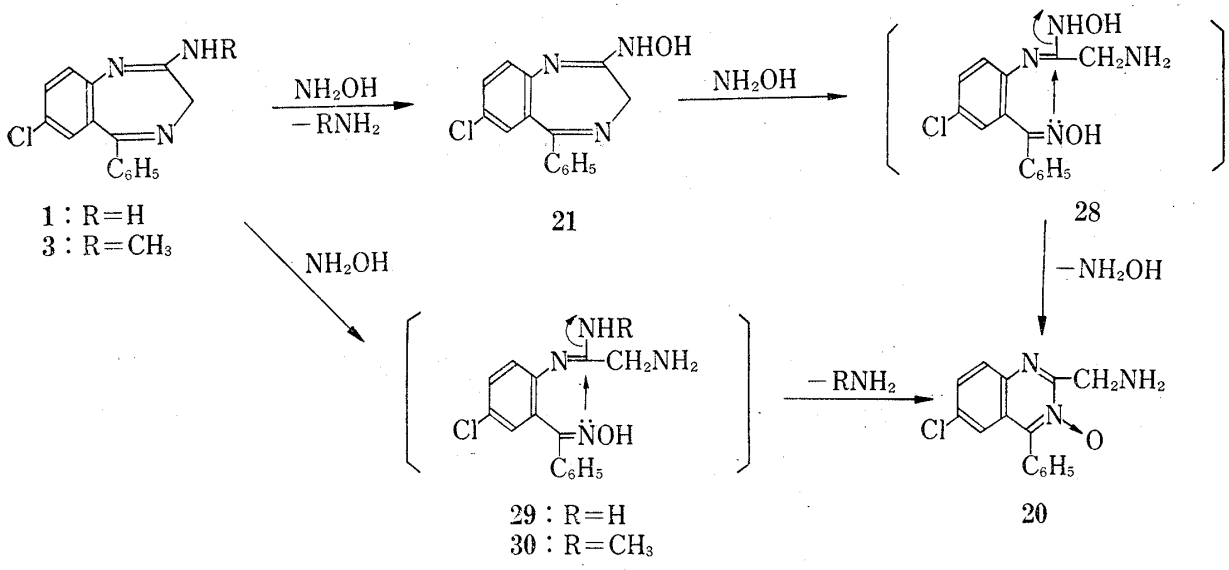


Chart 3

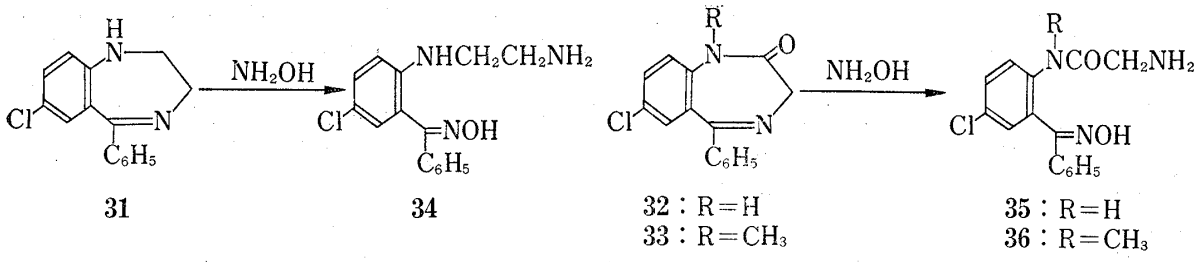


Chart 4

When the same reaction was applied to the 4N-oxide (**2**), in which the N-4: C-5 double bond should be less susceptible to attack by hydroxylamine, a 2-hydroxyamino derivative (**37**) was obtained in good yield as expected. Treatment of **37** with phosphorus trichloride gave **21**. Reduction of **37** with zinc in acetic acid afforded **24** and acetylation of **37** gave the O-acetate (**38**). Cyclization of **37** with phosgene afforded the oxadiazolo[4,3-*a*][1,4]benzodiazepine 5-oxide (**39**). Treatment of **38** and **39** with phosphorus trichloride afforded **23** and **25**, respectively.

However when the 2-methylamino analog of **2**, compound **4**, was treated with hydroxylamine hydrochloride, a quinazoline-2-carboxaldehyde oxime 3-oxide (**40**) was obtained in 20% yield in addition to **37** (45%). Compound **40** gave an O-acetate (**41**) on acetylation. Treatment of **40** with phosphorus trichloride furnished a dehydrated and deoxygenated compound with an empirical formula $C_{15}H_8N_3Cl$. This compound had an IR absorption band at 2250 cm^{-1} attributable to a cyano group and was found to be identical with a 2-cyanoquinazoline (**42**) which was synthesized unequivocally from a quinazoline-2-carboxaldehyde (**44**)[12] by oximation followed by dehydration. The structure **40** is thus clearly established from these chemical transformations.

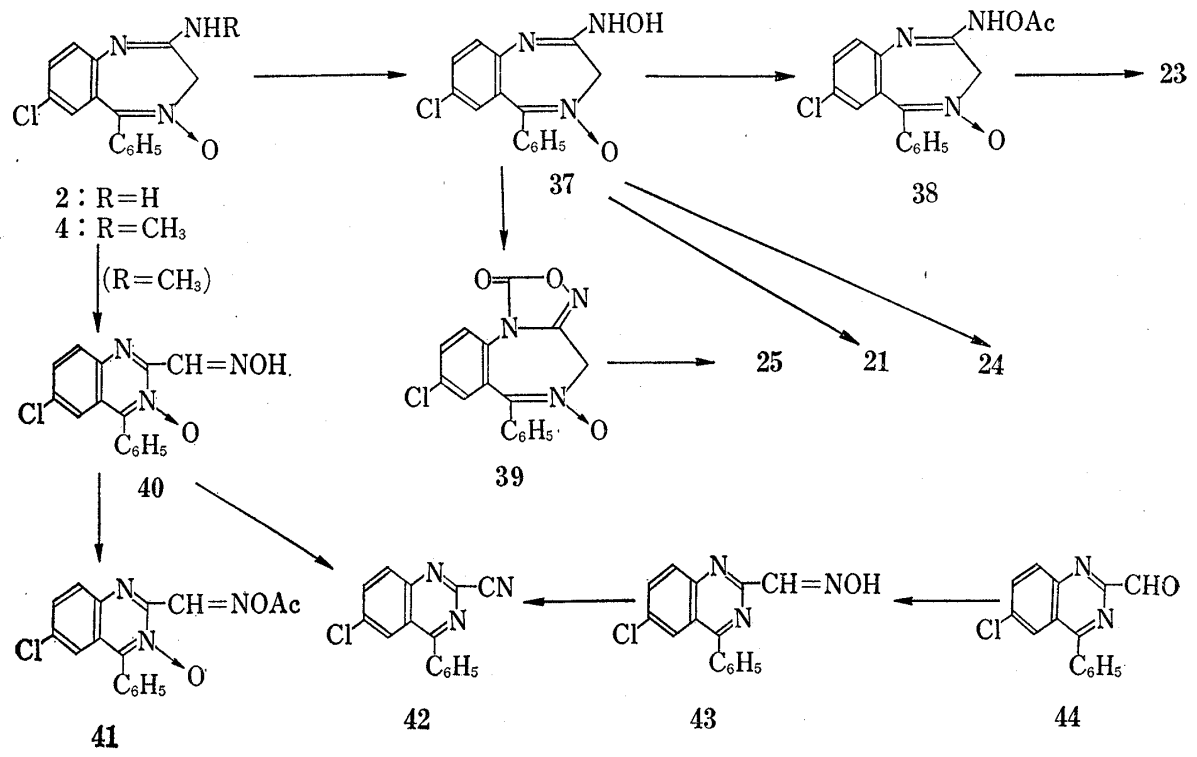


Chart 5

The formation of **40** may also be attributed to ring opening at the N-4: C-5 double bond. The lower susceptibility of C-2 to nucleophilic attack in **4** than in **2** would favor the ring-opening reaction. A plausible reaction mechanism for the formation of **40** is illustrated in Chart 6.

As we already communicated,[13] we found that the reaction of 2-amino-1,4-benzodiazepines with hydrazine also gave substituted 2-hydrazino-1,4-benzodiazepines. These results will be detailed in a subsequent paper.

12) L.H. Sternbach, E. Reeder, A. Stempel, and A.I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).
13) K. Meguro and Y. Kuwada, *Tetrahedron Letters*, **1970**, 4039.

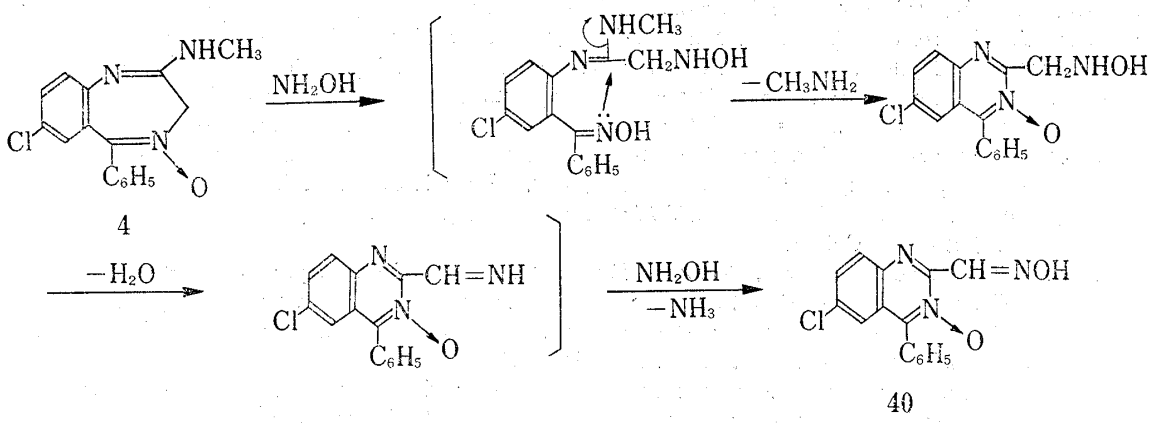


Chart 6

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured on a Hitachi 215 spectrophotometer, UV spectra on a Perkin-Elmer 450 spectrophotometer, nuclear magnetic resonance (NMR) spectra on a Varian A-60 or Varian T-60 spectrometer using tetramethylsilane as an internal standard, and mass spectra on a Hitachi RMU-6D double focussing mass spectrometer using a direct sample inlet system. The following abbreviations are used; s=singlet, d=doublet, b=broad. Removal of solvents was performed on a rotary evaporator under water aspirator pressure. When a compound was prepared by separate routes, their identity was established by a comparison of their IR spectra.

2-Substituted-amino Derivatives of 5-Phenyl-3*H*-1,4-benzodiazepines (3—13, Table I)——These compounds were prepared according to one of the following methods. After completion of the reaction, the reaction mixture was concentrated and then diluted with H_2O. The products were isolated by filtration or by extraction with $CHCl_3$ or AcOEt and recrystallized.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (3)——Method A: A mixture of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine[3] (1, 5.4 g), methylamine hydrochloride (13.5 g) and EtOH (240 ml) was refluxed for 2.5 hr, concentrated, and diluted with H_2O. The resulting precipitate was collected by filtration, washed with H_2O, and dried to give 3 (4.9 g), mp 233—235°. Recrystallization from Me_2CO gave pale yellow prisms, mp 240—241°.

7-Chloro-2-(2-hydroxyethyl)amino-5-phenyl-3*H*-1,4-benzodiazepine (6)——Method B: A mixture of crude dihydrochloride[3] of 1 (3.4 g), monoethanolamine (3.1 g) and MeOH (100 ml) was refluxed for 4 hr. The mixture was concentrated, diluted with H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent followed by addition of ether gave 6 (2.7 g), mp 169—171°. Recrystallization from ether gave colorless needles, mp 172—173°.

7-Chloro-2-ethoxycarbonylmethylamino-5-phenyl-3*H*-1,4-benzodiazepine (10)——Method C: A mixture of 1 (1.35 g), glycine ethyl ester hydrochloride (2.1 g), 2-methylimidazole (1.23 g) and EtOH (50 ml) was refluxed for 1.5 hr. The mixture was concentrated, diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the extract was recrystallized from *n*-hexane to give **10** (1.1 g), mp 95—96°.

2-Alkoxyamino-5-phenyl-3*H*-1,4-benzodiazepines (14—19, Table I)——These compounds were prepared according to one of the following methods. The products were isolated from the reaction mixture and recrystallized.

2-Benzyloxyamino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (14)——Method D: A mixture of **1** (406 mg), O-benzylhydroxylamine (550 mg), MeOH (15 ml) and AcOH (0.27 ml) was refluxed for 15 min and concentrated to dryness. The crystalline residue was collected and washed with MeOH to give **14** (405 mg), mp 178—180°. Recrystallization from MeOH gave colorless needles, mp 180—182°.

7-Chloro-2-methoxyamino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (15)——Method E: A mixture of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide[5] (2, 275 mg), O-methylhydroxylamine hydrochloride (170 mg) and EtOH (8 ml) was refluxed for 30 min. After evaporation of the solvent the residue was partitioned between saturated aq. $NaHCO_3$ and $CHCl_3$. The organic phase was treated in the usual manner to afford **15** (250 mg), mp 229—230°. Recrystallization from MeOH gave colorless prisms of mp 229—231°.

2-Benzyloxyamino-7-nitro-5-phenyl-3*H*-1,4-benzodiazepine (19)——Method F: A mixture of 2-amino-7-nitro-5-phenyl-3*H*-1,4-benzodiazepine dihydrochloride[3] (706 mg), O-benzylhydroxylamine (740 mg) and MeOH (20 ml) was refluxed for 30 min. After cooling, the precipitate was collected by filtration and the filtrate was concentrated to obtain additional crystals. The combined crystals (185 mg) were recrystallized from MeOH as yellow needles, mp 215—216°.

2-Aminomethyl-6-chloro-4-phenylquinazoline 3-Oxide (**20**)——From **1** (see also Preparation of **21** in Method G): A mixture of **1** (543 mg), $NH_2OH \cdot HCl$ (420 mg) and MeOH (10 ml) was refluxed for 20 min and concentrated to dryness. The residue was partitioned between H_2O (30 ml) and AcOEt (5 ml). The aqueous phase containing **20** hydrochloride was separated, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave **20** (420 mg, 74%). Recrystallization from MeOH–ether afforded colorless needles, mp 165—167° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}ON_3Cl$: C, 63.04; H, 4.23; N, 14.70. Found: C, 62.78; H, 4.13; N, 14.43. Ninhydrin (+). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3290 (NH_2). UV λ_{max}^{EtOH} nm (ε): 231 (26600), 264 (28200). NMR ($CDCl_3$) δ: 1.93 (2H, bs, NH_2), 4.37 (2H, s, $-CH_2-$).

From **3**: To a suspension of **3** (285 mg) in MeOH (6 ml) was added in portions $NH_2OH \cdot HCl$ (210 mg) with stirring. The mixture was stirred at room temperature for 30 min, poured into aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was treated in the usual manner and the product (**20**) was crystallized from ether as colorless crystals (235 mg, 82%), mp 164—165°.

When the mother liquor was evaporated and the residue purified by a column chromatography on silica gel, compound **21** (*vide infra*) was obtained as a powder (15 mg. 5%), mp 135°.

From **21**: A mixture of **21** (200 mg), $NH_2OH \cdot HCl$ (180 mg) and MeOH (5 ml) was refluxed for 30 min and concentrated to dryness. To the residue was added saturated aq. $NaHCO_3$ and the mixture was extracted with AcOEt. Evaporation of the solvent gave **20** (110 mg, 55%), mp 158—161° (decomp.).

7-Chloro-2-hydroxyamino-5-phenyl-3*H*-1,4-benzodiazepine (**21**)——From **1** (Method G): To a suspension of **1** (270 mg) in MeOH (6 ml), $NH_2OH \cdot HCl$ (210 mg) was added portionwise with stirring and cooling at 0—10° and stirring was continued at the same temperature for 15 min. The resulting solution was poured into saturated aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue treated with a mixture of acetone–*n*-hexane to give a pale yellow powder (250 mg) which was a mixture of **21** and **20**. The products were separated by a column chromatography on silica gel (20 g) using a solvent system $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as eluent. The eluate containing **21** was evaporated and treated with ether–*n*-hexane to give a colorless powder (200 mg, 70%), mp 136—138° (lit.[8] mp 126—130°). $FeCl_3$ (+). NMR ($CDCl_3$) δ: 4.35 (2H, s, $-CH_2-$). Mass Spectrum: *m/e* 285 (M^+).

The eluate containing **20** was evaporated and recrystallized from ether to give colorless crystals (30 mg, 10.5%), mp 163—165°.

From **3**: See preparation of **20** from **3** (*vide supra*).

From **37**: A mixture of **37** (500 mg), $CHCl_3$ (20 ml) and PCl_3 (0.6 ml) was refluxed for 20 min. To the solution were added H_2O and 30% NaOH with cooling and the organic layer was separated, washed with H_2O, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by a column chromatography on silica gel to give **21** as a powder (90 mg, 16.5%), mp 130°.

2-Acetamidomethyl-6-chloro-4-phenylquinazoline 3-Oxide (**22**)——A solution of **20** (370 mg) in Ac_2O (1.5 ml) was stirred at room temperature for 5 min and the precipitate was collected and washed with ether to give **22** (300 mg). Recrystallization from acetone gave colorless needles, mp 218—220°. *Anal.* Calcd. for $C_{17}H_{14}O_2N_3Cl$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.48; H, 4.29; N, 12.72. IR ν_{max}^{KBr} cm^{-1}: 1650 (amide carbonyl). NMR ($CDCl_3$) δ: 2.08 (3H, s, $-COCH_3$), 4.94 (2H, d, J=5.6 Hz, $-C\underline{H}_2NH-$), *ca.* 6.9 (1H, b, NH).

2-Acetoxyamino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**23**)——From **21**: A solution of **21** (60 mg) in Ac_2O (0.3 ml) was allowed to stand at room temperature. After about 5 min the precipitate was collected by filtration and washed with ether to give **23** (40 mg). Recrystallization from acetone gave colorless needles of mp 201—203° (decomp.). *Anal.* Calcd. for $C_{17}H_{14}O_2N_3Cl$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.44; H, 4.29; N, 12.90. IR ν_{max}^{KBr} cm^{-1}: 1750 (ester carbonyl).

From **38**: A mixture of **38** (300 mg), $CHCl_3$ (10 ml) and PCl_3 (0.3 ml) was refluxed for 30 min. After evaporation of the solvent the residue was partitioned between $CHCl_3$ and 2N NaOH. The organic phase was separated and treated in the usual manner. The product was crystallized from ether as colorless crystals (135 mg, 47%), mp 201—203° (decomp.).

Hydrogenation of 21 Over Raney Nickel: Conversion of 21 to 1——Compound **21** (200 mg) was hydrogenated over Raney Ni (1 g, wet) in MeOH (10 ml) at room temperature and atmospheric pressure until no more hydrogen was absorbed. The catalyst was filtered off and the filtrate concentrated to give **1** as colorless prisms, mp 230—232° (decomp.). This was found to be identical with an authentic sample of **1** by IR comparison.

2-Amino-7-chloro-4,5-dihydro-5-phenyl-3*H*-1,4-benzodiazepine (**26**)——To a solution of **1** (5.4 g) in dry tetrahydrofuran (140 ml) $LiAlH_4$ (1.5 g) was added portionwise with stirring and the mixture was refluxed for 1.5 hr. Excess $LiAlH_4$ was decomposed by cautious addition of H_2O and the precipitate was removed by filtration. The filtrate was concentrated and extracted with $CHCl_3$ (50 ml×2). The extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent followed by crystallization from ether gave **26** as colorless crystals (2.5 g, 46%), mp 191—193° (decomp.). Recrystallization from AcOEt afforded colorless plates, mp 192—193.5° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}N_3Cl$: C, 66.29; H, 5.19; N, 15.46. Found: C, 66.19; H, 5.08; N, 15.31.

7-Chloro-4,5-dihydro-2-hydroxyamino-5-phenyl-3*H*-1,4-benzodiazepine (24)——From **26**: A mixture of **26** (250 mg), $NH_2OH \cdot HCl$ (210 mg) and MeOH (15 ml) was refluxed for 30 min and the solvent removed. The residue was partitioned between aq. $NaHCO_3$ and $CHCl_3$, and the organic phase separated and treated in the usual way. The product was crystallized from MeOH as colorless crystals (200 mg, 76%). Recrystallization from MeOH gave colorless needles, mp 192—194° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}ON_3Cl$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.51; H, 4.62; N, 14.56. $FeCl_3$ (+).

From **27**: Similarly, **24** was synthesized from 7-chloro-4,5-dihydro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**27**)[5] in 89% yield.

From **21**: To a stirred solution of **21** (200 mg) in AcOH (3 ml) was added zinc powder (100 mg) and the mixture was stirred at room temperature for 30 min. This was then poured into saturated aq. $NaHCO_3$ and extracted with $CHCl_3$. From the extract, **24** (80 mg, 40%) was isolated as colorless crystals, mp 190—191° (decomp.).

From **37**: To a stirred solution of **37** (300 mg) in AcOH (3 ml) was added zinc powder (200 mg). The mixture was stirred for 1 hr and filtered to remove insoluble matter. The filtrate was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with aq. $NaHCO_3$ and H_2O and dried over Na_2SO_4. Evaporation of the solvent gave colorless crystals (130 mg, 45%), mp 189—192° (decomp.).

8-Chloro-6-phenyl-1*H*, 4*H*[1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one (25)——From **21**: A solution of **21** (200 mg), N,N′-carbonylbis(2-methylimidazole) (200 mg) in $CHCl_3$ (10 ml) was stirred for 30 min, washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue crystallized from iso-Pr_2O to give **25** (150 mg, 69%). Recrystallization from iso-Pr_2O gave colorless fine needles, mp 151—152° (lit.[8] mp 191—192°). *Anal.* Calcd. for $C_{16}H_{10}O_2N_3Cl$: C, 61.64; H, 3.23; N, 13.48. Found: C, 61.81; H, 3.07; N, 13.41. IR ν_{max}^{KBr} cm^{-1}: 1775 (–CO–).

From **39**: A mixture of **39** (200 mg), $CHCl_3$ (5 ml) and PCl_3 (0.4 ml) was refluxed for 20 min. The solvent was evaporated and the residue partitioned between 20% KOH and $CHCl_3$. The organic layer was separated and treated in the usual manner to give an oil. This was purified by a column chromatography on silica gel using *n*-hexane–acetone (3: 2, v/v) as eluent. The product was recrystallized from iso-Pr_2O to yield colorless crystals (125 mg, 66%), mp 145—147°.

2-(2-Aminoethylamino)-5-chlorobenzophenone Oxime (34)——A solution of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine[9] (**31**, 256 mg) and $NH_2OH \cdot HCl$ (350 mg) in EtOH (10 ml) was refluxed for 2 hr. After removal of the solvent the residue was partitioned between aq. $NaHCO_3$ and $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4 and evaporated to afford crystals (260 mg), mp 115—120°, which may be a mixture of *syn* and *anti* isomers. Recrystallization from MeOH gave colorless needles (90 mg, 31%), mp 173—174°. *Anal.* Calcd. for $C_{15}H_{16}ON_3Cl$: C, 62.17; H, 5.57; N, 14.50. Found: C, 62.14; H, 5.53; N, 14.65. Ninhydrin (+).

The same compound (**34**), mp 173—174°, was obtained in 31% yield by fusing **31** and $NH_2OH \cdot HCl$ with 2-methylimidazole at 120—140° for 30 min.

2-Aminoacetamido-5-chlorobenzophenone Oxime (35)——A mixture of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**32**),[10] $NH_2OH \cdot HCl$ (220 mg) and EtOH (10 ml) was refluxed for 2.5 hr. The crystalline product (85 mg, 15.5%) obtained after the usual treatment was recrystallized from EtOH to yield colorless needles, mp 209—210° (lit.[11] reported for *anti* form of **21** hydrate: mp 190—191°; for the *syn*: mp 169—169.5°). *Anal.* Calcd. for $C_{15}H_{14}O_2N_3Cl$: C, 59.31; H, 4.61; N, 13.84. Found: C, 59.03; H, 4.59; N, 13.89. Ninhydrin (+). $FeCl_3$ (−). IR ν_{max}^{KBr} cm^{-1}: 1700 (amide carbonyl). Mass Spectrum: *m/e* 303 (M^+).

2-(N-Aminoacetyl-N-methyl)amino-5-chlorobenzophenone Oxime (36)——A mixture of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[10] (**33**, 2.0 g), $NH_2OH \cdot HCl$ (1.33 g) and EtOH (20 ml) was refluxed for 2 hr. The mixture was treated in the usual manner to obtain crystals (2.05 g, 82%). Recrystallization from EtOH gave colorless needles (1.45 g, 58%), mp 209—210° (lit.[11] reported for hydrate of N^1-methyl analog of **21**: mp 205° (decomp.)). *Anal.* Calcd. for $C_{16}H_{16}O_2N_3Cl$: C, 60.47; H, 5.07; N, 13.22. Found: C, 60.38; H, 4.90; N, 13.00. Ninhydrin (+). $FeCl_3$ (−). IR ν_{max}^{KBr} cm^{-1}: 1660 (amide carbonyl).

7-Chloro-2-hydroxyamino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (37)——From **2** (Method H): A mixture of **2** (275 mg), $NH_2OH \cdot HCl$ (210 mg) and MeOH (15 ml) was refluxed for 30 min, concentrated and diluted with H_2O. The precipitate was collected by filtration, washed with H_2O and dried to yield **37** (215 mg, 71.5%). Recrystallization from CH_2Cl_2–*n*-hexane gave colorless needles, mp 236—237° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_2N_3Cl$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.59; H, 3.88; N, 13.95. $FeCl_3$ (+). NMR (DMSO-d_6) δ: 4.54 (2H, b, $-CH_2-$), 9.45, 10.17 (each 1H, s, NHOH).

From **4**: See preparation of **40**.

2-Acetoxyamino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (38)——A suspension of **37** (300 mg) in Ac_2O (7 ml) was heated at 70° for 10 min. After cooling, the precipitate was collected by filtration and washed with ether to yield **38** (220 mg, 64%). Recrystallization from MeOH gave colorless plates, mp 236—237° (decomp.). *Anal.* Calcd. for $C_{17}H_{14}O_3N_3Cl$: C, 59.39; H, 4.10; N, 12.22. Found: C, 59.35; H, 3.78; N, 12.02. IR ν_{max}^{KBr} cm^{-1}: 1755 (ester). NMR (DMSO-d_6) δ: 2.18 (3H, s, $-COCH_3$), 4.3—4.9 (2H, b, $-CH_2-$), 10.0 (1H, s, NH). Treatment of **38** with HCl–MeOH regenerated **37**.

8-Chloro-6-phenyl-1*H*, 4*H*[1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one 5-Oxide (39)——To a stirred and ice-cooled mixture of 10%phosgene in toluene (0.8 ml) and dry tetrahydrofuran (10 ml) was added drop-

wise a solution of **31** (300 mg) and Et_3N (0.3 ml) in dry tetrahydrofuran (10 ml). The mixture was stirred for 45 min with cooling and filtered. The filtrate was concentrated to dryness and the residue partitioned between saturated aq. $NaHCO_3$ and $CHCl_3$. The organic phase was separated, washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent left a crystalline residue which was collected to yield **39** (260 mg, 80%). Recrystallization from Me_2CO–*n*-hexane gave colorless plates, mp 230—232° (decomp.). *Anal.* Calcd. for $C_{16}H_{10}O_3N_3Cl$: C, 58.63; H, 3.07; N, 12.82. Found: C, 58.80; H, 2.85; N, 12.66.

6-Chloro-4-phenylquinazoline-2-carboxaldehyde Oxime 3-Oxide (40)——A mixture of **4** (3.0 g), NH_2OH·HCl (3.5 g) and MeOH (70 ml) was refluxed for 45 min and the hot solution was filtered to collect the yellow crystalline precipitate of **40** (600 mg, 20%). Recrystallization from DMF–H_2O gave yellow fine plates, mp 244—245° (decomp.). *Anal.* Calcd. for $C_{15}H_{10}O_2N_3Cl$: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.30; H, 3.14; N, 13.90. NMR (DMSO-d_6) δ: 8.71 (1H, s, –CH=N–), 12.4 (1H, s, OH).

From the above filtrate compound **37** was isolated (1.35 g, 45%) as colorless needles, mp 238—240° (decomp.).

2-Acetoxyiminomethyl-6-chloro-4-phenylquinazoline 3-Oxide (41)——To a solution of **40** (500 mg) in DMF (11 ml) was added AcCl (0.25 ml) and the mixture was heated at 95° for 10 min. The reaction mixture was then poured into ice-water and the resulting precipitate was collected and washed with aq. $NaHCO_3$, H_2O and MeOH. Purification of the precipitate by a column chromatography on silica gel (10 g) using $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as eluent yielded **41** as yellow crystals (250 mg, 44%). Recrystallization from AcOEt gave yellow needles, mp 186—188°. *Anal.* Calcd. for $C_{17}H_{12}O_3N_3Cl$: C, 59.74; H, 3.54; N, 12.30. Found: C, 60.06; H, 3.46; N, 12.41. IR ν_{max}^{KBr} cm^{-1}: 1782 (ester).

6-Chloro-2-cyano-4-phenylquinazoline (42)——From **40**: Compound **40** (200 mg) was dissolved in 1 ml of PCl_3 (an exothermic reaction occurred) and the resulting solution was allowed to stand at room temperature for 30 min. After evaporation, 20% KOH was added to the residue and the mixture extracted with AcOEt. The extract was treated in the usual manner and concentrated to dryness. The crystalline residue was dissolved in a mixture of *n*-hexane and Me_2CO (3: 2, v/v) and passed through a column packed with silica gel (10 g). Concentration of the eluate gave crystals (120 mg, 67%) which was recrystallized from MeOH to yield colorless needles, mp 180—182°. *Anal.* Calcd. for $C_{15}H_8N_3Cl$: C, 67.80; H, 3.03; N, 15.81. Found: C, 67.80; H, 2.76; N, 15.77. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN).

From **43**: A solution of **43** (55 mg) in $POCl_3$ (1 ml) was heated at 95° for 15 min and concentrated to dryness. To the cooled residue was added 20% KOH and the mixture was extracted with AcOEt. The crude product obtained from the extract was purified by a column chromatography on silica gel and colorless crystals, mp 179—181°, were obtained (32 mg, 61.5%).

6-Chloro-4-phenylquinazoline-2-carboxaldehyde Oxime (43)——A solution of 6-chloro-4-phenylquinazoline-2-carboxaldehyde[12] (**44**, 135 mg), NH_2OH·HCl (70 mg) and AcONa (80 mg) in EtOH (8 ml) was refluxed for 45 min, concentrated, and diluted with H_2O. The product was collected by filtration and recrystallized from MeOH to give colorless needles (110 mg, 77.5%), mp 243—244° (decomp.). *Anal.* Calcd. for $C_{15}H_{10}ON_3Cl$: C, 63.49; H, 3.55; N, 14.81. Found: C, 63.47; H, 3.30; N, 14.85.

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