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

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(Received December 18, 1972)

Substitution of the amino group of 2-amino-3H-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-hydroxymino-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 (23 and 39).

In a previous paper, 5) we reported a new method for the synthesis of 2-amino-3H-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 6) 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-3H-1,4-benzodiazepine (1) 7) was heated with methylamine hydrochloride in ethanol, the 2-methylamino derivative (3) was obtained in 86% yield. Under similar conditions, the 4N-oxide (2) 8) 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°C) compound 21 predominated (70%).

2) Location: Joso, Higashiyodogawa-ku, Osaka, Japan.
### Table I. 2-Substituted-1,4-benzodiazepines

![Chemical structure image]

| Compd. No. | R₁ | R₂ | X | R | Recrystn. from | mp (°C)
|------------|----|----|---|---|----------------|---------
| 3          | Cl | H  | Me| Me| Ac             | 240–241<sup>b</sup> |
| 4          | Cl | H  | O | Me| EtOH           | 235–236<sup>b</sup> |
| 5          | H  | H  | n-Bu | (CH₂)₄OH | Eth-PE         | 130–131 |
| 6          | Cl | H  | (CH₂)₄OH | Eth | AcOEt         | 203–205 |
| 7          | Cl | H  | (CH₂)₄NEt₂ | THF-Eth | IPE       | 159–160 |
| 8          | Cl | H  | CH₃COOEt | IPE | 97–98         |
| 9          | Cl | H  | CH₃COOEt | IPE | 150–151       |
| 10         | NO₂ | H  | (CH₂)₃NMe₂ | MeOH | 130–132       |
| 11         | NO₂ | H  | CH₃COOEt | Ac-H | 104–194       |
| 12         | Cl | H  | OCH₃C₆H₅ | MeOH | 180–182       |
| 13         | Cl | H  | OCH₃C₆H₅ | MeOH | 229–231       |
| 14         | Cl | H  | OCH₃C₆H₅ | MeOH | 220–222       |
| 15         | Cl | H  | OCH₃C₆H₅ | B   | 192–194       |
| 16         | NO₂ | H  | OCH₃C₆H₅ | MeOH | 179–180       |
| 17         | Cl | H  | OCH₃C₆H₅ | MeOH | 215–216       |
| 18         | Cl | H  | OH | Eth-H | 136–138<sup>b</sup> |
| 19         | Cl | H  | OH | Eth-H | 236–237(d.) |

### Analysis (%)

<table>
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<tr>
<th>Compd. No.</th>
<th>Yield, %</th>
<th>Formula</th>
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<th>H</th>
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<sup>b</sup> uncorrected.
<sup>c</sup> See Experimental Section.
<sup>d</sup> lit. mp 240–241°.
<sup>e</sup> lit. mp 236–236.5°.
<sup>f</sup> diprivate.
<sup>g</sup> This was the result from a single experiment and no attempts were made to obtain optimum yields.
<sup>h</sup> powdery compound (lit. mp 126–130°) Mass Spectrum: m/e 318 (M⁺).
Compound 20, which analyzed for C_{15}H_{16}O_{9}N_{2}Cl, 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-chloromethyl-4-phenyquinazoline 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 oxazadiol-4,3-a[1,4]benzodiazepine (25)\(^9\) was synthesized from 21 by the reaction with N,N'-carbonylbis(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-1H-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\(^12\) were obtained.

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8) This compound has recently been reported by J.B. Hester, Jr., D.J. Duchamp and C.G. Chidester, *Tetrahedron Letters*, 1971, 1609.
11) During the course of our investigation, the synthesis of hydrates of a 2-hydroxymino-1,4-benzodiazepine (21) and its N-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.
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 \( \text{C}_{12}\text{H}_7\text{N}_3\text{Cl} \). 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)\(^{19}\) by oximation followed by dehydration. The structure 40 is thus clearly established from these chemical transformations.

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.

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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 focusing 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-3H-1,4-benzodiazepines (3–13, Table 1) — 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 H2O. The products were isolated by filtration or by extraction with CHCl3 or AcOEt and recrystallized.

7-Chloro-2-methylaminio-5-phenyl-3H-1,4-benzodiazepine (3) — Method A: A mixture of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine9) (1, 5.4 g), methylamine hydrochloride (13.5 g) and EtOH (240 ml) was refluxed for 2.5 hr, concentrated, and diluted with H2O. The resulting precipitate was collected by filtration, washed with H2O, and dried to give 3 (4.9 g), mp 233–235°. Recrystallization from Me2CO gave pale yellow prisms, mp 240–241°.

7-Chloro-2-(2-hydroxyethyl)aminio-5-phenyl-3H-1,4-benzodiazepine (6) — Method B: A mixture of crude dihydrochloride9) of 1 (3.4 g), monoethanolamine (3.1 g) and MeOH (100 ml) was refluxed for 4 hr. The mixture was concentrated, diluted with H2O, and extracted with CHCl3. The extract was washed with H2O and dried over Na2SO4. Evaporation of the solvent followed by addition of ether gave 6 (2.7 g), mp 168–171°. Recrystallization from ether gave colorless needles, mp 172–173°.

7-Chloro-2-[2-methoxy-carbonyl-methylaminio]-5-phenyl-3H-1,4-benzodiazepine (10) — Method C: A mixture of 1 (1.55 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 H2O and extracted with CHCl3. The crude product obtained from the extract was recrystallized from n-hexane to give 10 (1.1 g), mp 95–96°.

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

2-Benzoxylaminio-7-chloro-5-phenyl-3H-1,4-benzodiazepine (14) — Method D: A mixture of 1 (406 mg), O-benzoxylaldehyde (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-methoxyaminio-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (15) — Method E: A mixture of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide9) (2, 275 mg), O-methyloxylaldehyde hydrochloride (170 mg) and EtOH (8 ml) was refluxed for 30 min. After evaporation of the solvent the residue was partitioned between saturated aq. NaHCO3 and CHCl3. 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-Benzoxylaminio-7-nitro-5-phenyl-3H-1,4-benzodiazepine (19) — Method F: A mixture of 2-amino-7-nitro-5-phenyl-3H-1,4-benzodiazepine dihydrochloride9) (706 mg), O-benzoxylaldehyde (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], NH₂OH-HCl (420 mg) and MeOH (10 ml) was refluxed for 20 min and concentrated to dryness. The residue was partitioned between H₂O (30 ml) and AcOEt (5 ml). The aqueous phase containing 20 hydrochloride was separated, made alkaline with NaHCO₃, and extracted with CHCl₃. The extract was washed with H₂O and dried over Na₂SO₄. Evaporation of the solvent gave 20 (420 mg, 74%). Recrystallization from MeOH-ether afforded colorless needles, mp 165—167°C (decomp.). Anal. Calcd. for C₃H₃O₇Cl: C, 63.04; H, 4.23; N, 14.70. Found: C, 62.78; H, 4.13; N, 14.43. Ninhydrin (+). IR νmax cm⁻¹: 3350, 3290 (NH₂). UV λmax nm (ε): 231 (26600), 264 (28200). NMR (CDCl₃) δ: 1.93 (2H, bs, NHC₂H₃), 4.37 (2H, s, -CH₂-).

From 3: To a suspension of 3 (285 mg) in MeOH (6 ml) was added in portions NH₂OH-HCl (210 mg) with stirring. The mixture was stirred at room temperature for 30 min, poured into aq. NaHCO₃ and extracted with CHCl₃. 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°C.

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°C.

From 21: A mixture of 21 (200 mg), NH₂OH-HCl (180 mg) and MeOH (5 ml) was refluxed for 30 min and concentrated to dryness. To the residue was added saturated aq. NaHCO₃ and the mixture was extracted with AcOEt. Evaporation of the solvent gave 21 (110 mg, 55%), mp 158—161°C (decomp.).

7-Chloro-2-hydroxyamino-5-phenyl-1,4-benzodiazepine (21) — From 1 (Method G): To a suspension of 1 (270 mg) in MeOH (6 ml), NH₂OH-HCl (210 mg) was added portionwise with stirring and cooling at 0—10°C and stirring was continued at the same temperature for 15 min. The resulting solution was poured into saturated aq. NaHCO₃ and extracted with AcOEt. The extract was washed with H₂O and dried over Na₂SO₄. The solvent was evaporated and the residue treated with a mixture of acetone-9-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 CHCl₃-MeOH-AcOEt (85: 10: 5, v/v/v) as eluent. The eluate containing 21 was evaporated and treated with ether-9-hexane to give a colorless powder (200 mg, 70%), mp 136—138°C (lit.9 mp 126—130°C). FeCl₃ (+). NMR (CDCl₃) δ: 4.35 (2H, s, -CH₂-). Mass Spectrum: m/z 285 (M+).

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

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

From 37: A mixture of 37 (500 mg), CHCl₃ (20 ml) and PCl₅ (0.6 ml) was refluxed for 20 min. To the solution were added H₂O and 30% NaOH with cooling and the organic layer was separated, washed with H₂O, and dried over Na₂SO₄. 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 190°C.

2-Acetamidomethyl-6-chloro-4-phenylquinazoline 3-Oxide (22) — A solution of 20 (370 mg) in AcO (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°C. Anal. Calcd. for C₂₅H₂₁O₆N₄Cl: C, 52.29; H, 3.40; N, 12.82. Found: C, 52.48; H, 3.29; N, 12.72. IR νmax cm⁻¹: 1650 (amide carbonyl). NMR (CDCl₃) δ: 2.08 (3H, s, -COCH₃), 4.94 (2H, d, J = 5.6 Hz, -CH₂NH⁻), ca. 6.9 (1H, h, NHi).

2-Acetoxymino-7-chloro-5-phenyl-1,4-benzodiazepine (23) — From 21: A solution of 21 (60 mg) in AcO (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°C (decomp.). Anal. Calcd. for C₂₅H₂₁O₆N₄Cl: C, 52.29; H, 3.40; N, 12.82. Found: C, 52.44; H, 4.29; N, 12.90. IR νmax cm⁻¹: 1750 (ester carbonyl).

From 38: A mixture of 38 (300 mg), CHCl₃ (10 ml) and PCl₅ (0.3 ml) was refluxed for 30 min. After evaporation of the solvent the residue was partitioned between CHCl₃ 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°C (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°C (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-1,4-benzodiazepine (26) — To a solution of 1 (5.4 g) in dry tetrahydrofuran (140 ml) LiAlH₄ (1.5 g) was added portionwise with stirring and the mixture was refluxed for 1.5 hr. Excess LiAlH₄ was decomposed by cautious addition of H₂O and the precipitate was removed by filtration. The filtrate was concentrated and extracted with CHCl₃ (50 ml x 2). The extract was washed with H₂O and dried over Na₂SO₄. Evaporation of the solvent followed by crystallization from ether gave 26 as colorless crystals (2.5 g, 46%), mp 191—193°C (decomp.). Recrystallization from AcOEt afforded colorless plates, mp 192—193.5°C (decomp.). Anal. Calcd. for C₂₅H₂₃N₂Cl: C, 66.29; H, 5.19; N, 15.48. Found: C, 66.19; H, 5.08; N, 15.31.
7-Chloro-4,5-dihydro-2-hydroxyaminoo-5-phenyl-3H-1,4-benzodiazepine (24)—From 26: A mixture of 26 (250 mg), NH₂OH·HCl (210 mg) and MeOH (15 ml) was refluxed for 30 min and the solvent removed. The residue was partitioned between aq. NaHCO₃ and CHCl₃, 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 C₁₇H₁₄O₂N₂Cl: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.51; H, 4.62; N, 14.56. FeCl₃ (+).*

From 27: Similarly, 24 was synthesized from 7-chloro-4,5-dihydro-2-methyloaminoo-5-phenyl-3H-1,4-benzodiazepine (27)⁹ 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. NaHCO₃ and extracted with CHCl₃. 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 H₂O and evaporated with CHCl₃. The extract was washed with aq. NaHCO₃ and H₂O and dried over Na₂SO₄. Evaporation of the solvent gave colorless crystals (130 mg, 45%), mp 189—192° (decomp.).

8-Chloro-6-phenyl-1H, 4H[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-methyldiazole) (200 mg) in CHCl₃ (10 ml) was stirred for 30 min, washed with H₂O, and dried over Na₂SO₄. The solvent was evaporated and the residue crystallized from iso-Pr₂O to give 25 (150 mg, 65%). Recrystallization from iso-Pr₂O gave colorless fine needles, mp 151—152° (lit.⁸ mp 191—192°). *Anal. Calcd. for C₂₅H₂₄O₂N₂Cl: C, 61.64; H, 3.23; N, 13.48. Found: C, 61.81; H, 3.07; N, 13.41. IR νₓmax cm⁻¹: 1775 (C=O).*

From 39: A mixture of 39 (200 mg), CHCl₃ (5 ml) and PCl₃ (0.4 ml) was refluxed for 20 min. The solvent was evaporated and the residue partitioned between 20% KOH and CHCl₃. 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-Pr₂O 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-1H, 1,4-benzodiazepine⁹ (31, 256 mg) and NH₂OH·HCl (350 mg) in EtOH (10 ml) was refluxed for 2 hr. After removal of the solvent the residue was partitioned between aq. NaHCO₃ and CHCl₃. The organic phase was washed with H₂O, dried over Na₂SO₄ and evaporated to afford crystals (260 mg), mp 115—120°, which is a mixture of syn and anti isomers. Recrystallization from MeOH gave colorless needles (90 mg, 31%), mp 173—174°. *Anal. Calcd. for C₁₉H₁₇O₂N₂Cl: 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 NH₂OH·HCl with 2-methylimidazole at 120—140° for 30 min.

2-Aminocetamido-5-chlorobenzophenone Oxime (35)—A mixture of 7-chloro-3,4-dihydro-5-phenyl-2H, 1,4-benzodiazepin-2-one (32),¹⁰ NH₂OH·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 189—169.5°). *Anal. Calcd. for C₁₇H₁₆O₂N₂Cl: C, 59.31; H, 4.61; N, 13.84. Found: C, 59.03; H, 4.59; N, 13.89. Ninhydrin (+). FeCl₃ (-). IR νₓmax cm⁻¹: 1700 (amide carboxyl). 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-2H, 1,4-benzodiazepin-2-one (33),²⁰ NH₂OH·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.¹² reported for hydrate of N₁-methyl analog of 21: mp 205° (decomp.). *Anal. Calcd. for C₁₇H₁₇O₂N₂Cl: C, 60.47; H, 5.07; N, 13.22. Found: C, 60.38; H, 4.90; N, 13.00. Ninhydrin (+). FeCl₃ (-). IR νₓmax cm⁻¹: 1660 (amide carbonyl).*

7-Chloro-2-hydroxyaminoo-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (37)—From 2 (Method H): A mixture of 2 (275 mg), NH₂OH·HCl (210 mg) and MeOH (15 ml) was refluxed for 30 min, concentrated and diluted with H₂O. The precipitate was collected by filtration, washed with H₂O and dried to yield 37 (215 mg, 71.5%). Recrystallization from CH₂Cl₂-n-hexane gave colorless plates, mp 236—237° (decomp.). *Anal. Calcd. for C₁₇H₁₄O₂N₂Cl: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.59; H, 3.88; N, 13.95. FeCl₃ (+). NMR (DMSO-d₆) δ: 4.54 (2H, b, -CH₂-), 9.45, 10.17 (each 1H, s, NH₃H). From 4: See preparation of 40.

2-Acetoxyaminoo-7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (38)—A suspension of 37 (300 mg) in Ac₂O (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 C₁₇H₁₄O₂N₂Cl: C, 59.39; H, 4.10; N, 12.22. Found: C, 59.35; H, 3.78; N, 12.02. IR νₓmax cm⁻¹: 1755 (ester). NMR (DMSO-d₆) δ: 2.18 (3H, s, -COCH₃), 4.34—4.9 (2H, b, -CH₂-), 10.0 (1H, s, NH). Treatment of 38 with HCl—MeOH regenerated 37.

8-Chloro-6-phenyl-1H, 4H[1,2,4]oxadiazolo[4,3-a][1,4]benzodiazepin-1-one 5-Oxide (39)—To a stirred and ice-cooled mixture of 10% pho sene in toluene (0.8 ml) and dry tetrahydrofuran (10 ml) was added drop-
wise a solution of 3I (300 mg) and Et₃N (0.3 ml) in dry tetrathydrofuran (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. NaHCO₃ and CHCl₃. The organic phase was separated, washed with H₂O, and dried over Na₂SO₄. Evaporation of the solvent left a crystalline residue which was collected to yield 39 (260 mg, 80%). Recrystallization from Me₂CO–n-hexane gave colorless plates, mp 230–232° (decomp.). Anal. Calcd. for C₁₆H₁₀O₃N₃Cl: 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), NH₂OH.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–H₂O gave yellow fine plates, mp 244–245° (decomp.). Anal. Calcd. for C₁₆H₁₀O₃N₃Cl: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.30; H, 3.14; N, 13.90. NMR (DMSO-d₆) δ: 8.71 (1H, s, −CH=N−), 12.4 (1H, s, OH).

From the above filtrate compound 37 was isolated (135 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. NaHCO₃, H₂O and MeOH. Purification of the precipitate by a column chromatography on silica gel (10 g) using CHCl₃–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 C₁₇H₁₂O₃N₃Cl: C, 59.74; H, 3.54; N, 12.30. Found: C, 60.00; H, 3.46; N, 12.41. IR νₓmax cm⁻¹: 1782 (ester).

6-Chloro-2-cyano-4-phenylquinazoline (42)—From 40: Compound 40 (200 mg) was dissolved in 1 ml of PCl₅ (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 Me₂CO (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 C₁₇H₁₂N₃Cl: C, 67.80; H, 3.08; N, 15.81. Found: C, 67.80; H, 2.76; N, 15.77. IR νₓmax cm⁻¹: 2250 (CN).

From 43: A solution of 43 (55 mg) in PCl₅ (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 (44, 135 mg), NH₂OH.HCl (70 mg) and AcONa (80 mg) in EtOH (8 ml) was refluxed for 45 min, concentrated, and diluted with H₂O. 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 C₁₅H₁₆O₃N₃Cl: C, 63.49; H, 3.55; N, 14.81. Found: C, 63.47; H, 3.30; N, 14.85.

Acknowledgement We are very grateful to Dr. S. Tatsukawa, Director of this Division, for his encouragement throughout this work. We also thank to the members of the Analytical Section of this Laboratories for microanalyses and measurement of UV, NMR and mass spectra, and to Messrs. H. Miyano and Y. Sato for their technical assistance.