Reaction of 1-Methyl-4-phenylquinazolinium Salts with Diazomethane

Yoshihisa YAMADA, Toyonari OINE, and Ichizo INOUE

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., Kashima-cho, Higashiyodogawa-ku, Osaka 532

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For the synthesis of 5-phenyl-1,4-benzodiazepines, reaction of quinazolinium salts with diazomethane was studied. In the course of the study, it was found by NMR spectroscopy that the starting materials (**2**) reacted even with a slight amount of water present in the solvent to give hydrates **5**. Treatment of **2c** with diazomethane at 10 °C under absolute anhydrous conditions gave quinazoline **8c** and benzodiazepines **9** and **10c** in about the same ratio. In the reactions at lower temperatures, the distribution of the products varied markedly, and the ring expansion product **10c** was obtained in an improved yield. The mechanism for the formation of **8**, **9**, and **10** was discussed.

Within the past decade the synthesis of the 1,4-benzodiazepines has attracted considerable attention since the advent of chlorodiazepoxide and diazepam as tranquilizers,[1] and a number of synthetic approaches[2] to 1,4-benzodiazepine derivatives have been developed. In a previous paper,[3] we have reported that reaction of 1-methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium bromide with diazomethane in ethanol gave 1-methyl-3-ethoxy-4-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5*H*-one. We considered that this ring expansion reaction could become a new approach to the preparation of 5-phenyl-1,4-benzodiazepine derivatives from 1-methyl-4-phenylquinazolinium salts (**2**). We present results concerning the ring-expansion reaction of **2** with diazomethane.

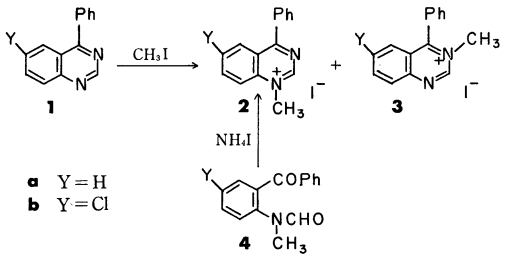


Chart 1.

The starting material, 1-methyl-4-phenylquinazolinium iodide (**2a**), has already been reported by Ott and Denzer.[4] They have observed that treatment of 4-phenylquinazoline (**1a**) with methyl iodide gave a mixture of the 1-methiodide (**2a**) and the 3-methiodide (**3a**) in a 7 : 1 ratio,[5] and that the two methiodides could not be separated by the usual purification technique because of their very similar physical properties. We reexamined the reaction thereby and found that the 1-methiodide could be easily isolated by washing with chloroform. The NMR spectrum of the product in DMSO-d_6 showed a couple of singlet at δ 3.80 and 4.60 (an intensity ratio of 1 : 10) assignable to two different *N*-methyl protons. The presence of the two *N*-methyl signals suggested an incomplete purification. However, since another set of two singlets (at δ 3.08 and 4.14[6]) observed in the spectrum of the original mixture has disappeared, we considered that one of the singlets might be due to the *N*-methyl protons of a contaminant. To ascertain this point, an unequivocal preparation of the 1-methiodide (**2a**) was attempted. Thermal cyclization of 2-(*N*-methylformamido)benzophenone (**4a**) with NH_4I in ethanol gave a product, albeit in a very low yield (4.3%), which showed an NMR spectrum identical with that of the purified 1-methiodide (**2a**) obtained according to Ott's procedure. Consequently, we concluded that the purified 1-methiodide (**2a**) was free from the 3-isomer and that, accordingly, one of the singlets was attributable to the *N*-methyl protons of the contaminant.

Quarternization of 4-phenyl-6-chloroquinazoline (**1b**) with methyl iodide also gave a mixture of a 1- and a 3-methiodide. The purified 1-methiodide (**2b**) exhibited a similar spectral pattern in its NMR spectrum. A presumption that the contaminant was the hydrated form of the 1-methiodide (**2b**) was proved by NMR spectroscopy (see Fig. 1 a, b, c). The hydration reaction of **2b** in DMSO-d_6 was carried out in an NMR sample tube. With an increase in the quantity of the additive water, the intensity of the

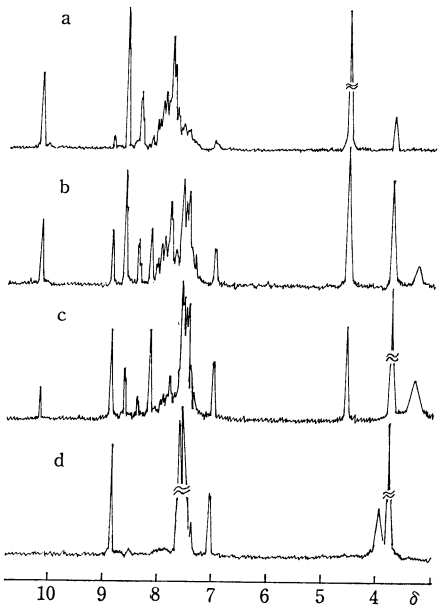
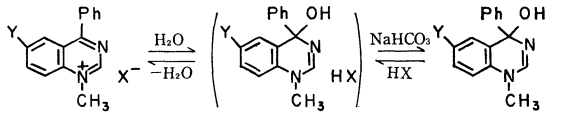


Fig. 1. NMR spectral change on hydration of **2b**.
- a The spectrum of **2b** (0.2 mmol) in DMSO-d_6 (0.6 ml).
- b The spectrum of **2b** (0.2 mmol) in DMSO-d_6 (0.6 ml) containing H_2O (0.056 mmol).
- c The spectrum of **2b** (0.2 mmol) in DMSO-d_6 (0.6 ml) containing H_2O (0.224 mmol).
- d The spectrum of **2b** (0.2 mmol) in DMSO-d_6 (0.6 ml) containing D_2O (0.1 ml).

singlet at δ 4.60 varied inversely; on the contrary, the methyl signal at δ 3.78 increased. Simultaneously, the signal at δ 10.20 assignable to $>\overset{+}{N}=CH-$ decreased an intensity in the same ratio, followed with enhancement of the signal at δ 8.91. The other important spectral feature was the disappearance of the doublet at δ 8.43 (J=2 Hz) corresponding to the aromatic proton on the 5-position in **2b** and the appearance of a new doublet at δ 7.05 (J=2 Hz). These high-field shifts was probably caused by the remission of the strong positive charge on the quinazolinium ring and the anisotropic effect of the benzene ring on the sp^3-C(4) formed upon hydration. Preferential occurrence of hydration at C(4) was supported by the absence of the coupling[7] between the hydroxy proton (δ 8.22) and the methine proton (δ 8.91) in the NMR spectrum in DMSO-d_6. The position of hydration may also be explained by a mechanistic consideration of the same type of reaction.[8] The methiodides (**2a-b**) were converted to 1-methyl-4-hydroxy-4-phenyl-1,4-dihydroquinazoline (**6**) and 1-methyl-4-hydroxy-4-phenyl-6-chloro-1,4-dihydroquinazoline (**7**) respectively under mild alkaline conditions. This conversion was found to be reversible. Thus, treatment of **6** and **7** with excess HBr afforded the corresponding quinazolinium bromides (**2c-d**) in a high yield.



2 a Y=H X=I **5** **6** Y=H
b Y=Cl X=I **7** Y=Cl
c Y=H X=Br
d Y=Cl X=Br

Chart 2.

Reaction of **2a-d** with diazomethane was carried out under absolute anhydrous conditions, because the nucleophilic attack of diazomethane to form an aziridinium compound can take place only at the iminium carbon.[9] Treatment of **2c** with diazomethane in anhydrous CH_2Cl_2 at 10 °C gave three major products in about the same ratio. The first product was characterized as a picrate; the structure was chemically confirmed as 1-methyl-2-bromomethyl-4-phenyl-1,2-dihydroquinazoline (**8c**) by hydrogenation with Raney nickel. The NMR spectrum of the hydrogenation product was consistent with 1,2-dimethyl-4-phenyl-1,2-dihydroquinazoline (**11**), exhibiting a doublet at δ 1.46 (J=6 Hz) assignable to the methyl group at the 2-position and an absence of any signals attributable to methylene protons. Two other products, 1-methyl-3-ethoxy-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**9**) and 1-methyl-3-bromomethyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**10c**) were isolated from the mother liquor by column chromatography. The structure of **9** was established by the presence of the characteristic absorption of 4-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine[10] at 242 nm (ε 22000) and at 346 (1700) in the UV spectrum and by the signal of an ethoxy group in the NMR spectrum. The structure of **10c** was tentatively assigned on the basis of the spectral data. The UV spectrum [242.5 nm (ε 23000) and 346 (2900)] corresponded to the datum for **9**. The bromomethyl group was indicated by the molecular ion peak (*m/e* 330 and 328) and the base peak (*m/e* 249) in the mass spectrum, and by a multiplet at δ 3.4—3.9 which overlapped with the endocyclic methylene and methine protons in the NMR spectrum. There remained a little ambiguity as to the position of the bromomethyl group.

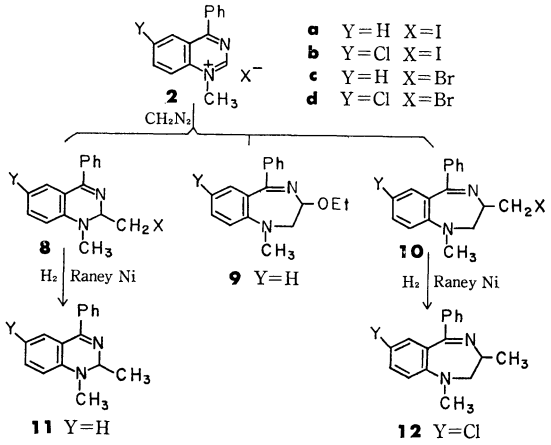


Chart 3.

Since the results of the preliminary reaction presented about was not necessarily satisfactory for our present purposes because of the low yield and the multiple product formation, we attempted to improve the reaction by changing the factors (the anion species, the

Table 1. Products in reaction of **2** with CH_2N_2

Exp. No	Y	X	Solv.	Temp. °C	Yield % 8	9	10
1	H	I	THF	10	69.4[a]		*[b]
2	H	Br	CH_2Cl_2	10	28.3[a]	13.1	11.0
3	H	Br	CH_2Cl_2	−20	*		74.2[c]
4	Cl	I	CH_2Cl_2	−35	24.5		46.6
5	Cl	Br	CH_2Cl_2	−45	*		55.3
6	H[d]	ClO_4	CH_2Cl_2	r. t.	—[e]	—	—

a) As the picrate. b) The tlc showed the presence of the compounds. However, since it seemed that the yields were very low, isolation was not attempted. c) As the picrolonate. d) 207—208 °C (decomp.). e) Nil.

substituent on the benzene ring, and the reaction conditions). Thus, the reactions of the quinazolinium salts (**2a–d**) with diazomethane were examined under various conditions. The results are shown in Table 1.

The reaction of 6-chloroquinazolinium iodide (**2b**) with diazomethane at −30——40 °C gave 1-methyl-2-iodomethyl-4-phenyl-6-chloro-1,2-dihydroquinazoline (**8b**) and 1-methyl-3-iodomethyl-5-phenyl-7-chloro-2,3-dihydro-1*H*-1,4-benzodiazepine (**10b**) in a ratio of about 1 : 2. The structure of **10b** was confirmed by its chemical transformation to a known compound, 1,3-dimethyl-5-phenyl-7-chloro-2,3-dihydro-1*H*-1,4 benzodiazepine (**12**).[11] Hydrogenation of **10b** with Raney nickel afforded **12** in a good yield. These results gave conclusive evidence for the tentative assignment of the structure of **10c**.

The change of the halide ion in the quinazolinium salt did not affect the product ratio. However, the reaction at low temperature showed a tendency to increase markedly the ratio of 3-halomethylbenzodiazepine. We will now attempt to explain the formation of **8**, **9**, and **10** (Chart 4). The process probably involves an initial attack of diazomethane to give an adduct (**A**) and a subsequent ring closure to the aziridinium halide (**B**). According to Crist and Leonard,[12] two pathways, a solvolysis-type reaction at the more substituted ring carbon and a nucleophilic displacement at the less hindered, less substituted ring carbon, are possible for the ring opening of an aziridinium compound. The product (**8**) would then be obtained by SN2-like ring opening with the halide ion at the less hindered methylene. However, an alternate route involving the displacement of the diazo group in (**A**) with the halide ion might be considered.

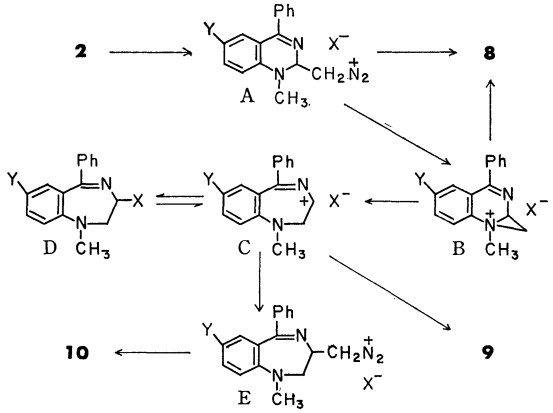


Chart 4.

The ring enlargement to **9** would be due to an *S*N1-type reaction of the most stable carbonium ion, which could arise *via* the ionic cleavage of the aziridinium intermediate (**B**), with the ethanol present in the ethereal diazomethane solution.[13] It seems that the formation of **10** was due to the participation of two equivalents of diazomethane. Bernhard and Snieckus[14] reported the formation of a benzazocine in addition to a seven-membered ring product in the reaction of 3,4-dihydro-2-methylisoquinolinium perchlorate with diazomethane. They explained the benzazocine formation by the second addition of diazomethane to the benzazepinium compound, which could arise from the aziridinium compound. However, the formation of our compound (**10**) could not be explained by their mechanism. Therefore, a different machanism must be operative in our case. Our failure to isolate the aziridinium compound (**B**) suggested that the intermediate (**B**) would be very unstable due to its own nature to afford smoothly the resonance-stabilized carbonium ion (**C**). This carbonium ion would react competitively with diazomethane and with the halide ion to give the adduct (**E**) and the halide (**D**) respectively. However, in view of the allylic nature of the C(3), the halide (**D**) would be amenable to equilibrium with the carbonium ion. Ultimately, the product (**10**) which could be formed *via* the displacement of the diazo group with the halide ion would become an end product.

The reaction of quinazolinium perchlorate with diazomethane was also attempted; however, it resulted only in the recovery of the starting material.

Experimental

Melting points are uncorrected and were determined on a Yamato apparatus, MP-1. The NMR spectra were determined on a Hitachi Perkin-Elmer R-20A instrument (Me_4Si). Mass spectra were measured on a Hitachi RMS-4 spectrometer. IR spectra were determined on a Shimadzu IR-27G spectrometer, and UV spectra, on a Hitachi EPS-2U spectrometer.

1-Methyl-4-phenyl-quinazolinium Iodide (2a). A): A mixture of 4-phenylquinazoline (**1**, 20.0 g) and methyl iodide (50 ml) was refluxed for 6 hr. The precipitates that had formed were collected by filtration and washed with Et_2O to give a crude product (21.0 g); mp 175—177 °C. In the NMR spectrum (DMSO-d_6), four singlets attributable to four different methyls (at δ 3.08, 3.80, 4.14, and 4.60) were observed.[6] The crude product was washed with $CHCl_3$ (300 ml) to give pure **2a** as an orange powder (15.5 g, 44.3%); mp 196—198 °C. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1590, 1520. NMR (DMSO-d_6) δ: 3.80 and 4.60 (3H, two singlets in the ratio of 1 : 10), 7.0—8.7 (9H, m), 8.86 and 10.15 (1H, two singlets in the ratio of 1 : 10). Found: C, 51.85; H, 3.77; N, 7.74%. Calcd for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76; N, 8.05%.

B): A mixture of 2-(*N*-methylformamido)benzophenone (**4a**, 0.5 g), NH_4I (0.5 g), and EtOH (10 ml) was heated in a sealed tube at 150—160 °C for 10 hr. The mixture was then concentrated to dryness, and the residue was triturated with AcOEt to give a crystalline material. The crystals were extracted with CH_2Cl_2 and the extract was concentrated. The residue was triturated with AcOEt to give **2a** (30 mg, 4.3%). The NMR spectrum of this compound was identical with that of **2a** prepared by Method A.

C): A mixture of 1-methyl-4-hydroxy-4-phenyl-1,4-dihydroquinazoline (**6**, 0.2 g), an excess of 57% HI (*ca.* 0.2 ml) and *i*-PrOH (10 ml) was warmed until it became a clear solution. After cooling, the precipitates were collected by filtration to give almost pure **2a** as orange leaflets (0.25 g, 89%); mp 195—197 °C (decomp.). The NMR spectrum and IR spectrum of this compound were identical with those of **2a**.

1-Methyl-4-phenyl-6-chloroquinazolinium Iodide (2b). A): A mixture of 4-phenyl-6-chloroquinazoline (**1b**, 11.0 g) and methyl iodide (30 ml) was heated in a sealed tube at 100—110 °C for 20 hr. The precipitates were collected by filtration and washed with Et_2O to give a crude product

(15.8 g, 97.7%); mp 204—205 °C (decomp.). NMR (DMSO-d_6) δ: 3.10 and 4.17 (two singlets, N^3-CH_3), 4.63 (s, N^1-CH_3) (3H, the ratio of 3 : 7),[15] 7.0—8.75 (8H, m), 8.99 and 9.95 (two singlets), 10.20 (s), (1H, the ratio of 3 : 7). This product was recrystallized from a mixture of DMF (100 ml) and AcOEt (50 ml) to give pure **2b** as dark red leaflets (8.6 g, 49.4%); mp 211—213 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1595, 1590, 1521. NMR: The spectrum is shown in Fig. 1. Found: C, 47.06; H, 3.10; N, 7.34%. Calcd for $C_{15}H_{12}N_2ClI$: C, 47.08; H, 3.17; N, 7.32%.

B): A mixture of 2-(*N*-methylformamido)-5-chlorobenzophenone (**4b**, 2.0 g), NH_4I (4.0 g), and EtOH (30 ml) was heated in a sealed tube at 150 °C overnight. The mixture was then concentrated to dryness, and the residue was triturated with AcOEt. The solid was collected by filtration and extracted with CH_2Cl_2 (100 ml). The extract was concentrated to give a crystalline residue (200 mg). A mixture of the residue (100 mg), three drops of 47% HI, and *i*-PrOH (5 ml) was warmed to give a clear solution. After cooling, the crystals which had formed were collected by filtration to give pure **2b** as red leaflets (50 mg, 3.5%); mp 212—213 °C (decomp.). The NMR spectrum of this compound was identical with that of **2b** prepared by Method A. **4b** (1.1 g, 55%) was recovered from the AcOEt filtrate.

*1-Methyl-4-hydroxy-4-phenyl-1,4-dihydroquinazoline (**6**).* To a suspension of **2a** (1.0 g) in H_2O (20 ml) was added $NaHCO_3$ (1.5 g), and the mixture was stirred at room temperature for 1 hr. The crystals were collected by filtration to give almost pure **6** (0.65 g, 95%); mp 135—136 °C (decomp.). Recrystallization from DMF-EtOH gave an analytical sample colorless leaflets; mp 141—143 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1600, 1570. NMR (DMSO-d_6) δ: 3.30 (3H, s), 6.22 (1H, br.s), 6.8—7.55 (10H, m). Found: C, 75.65; H, 5.92; N, 11.82%. Calcd for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76%.

*1-Methyl-4-hydroxy-4-phenyl-6-chloro-1,4-dihydroquinazoline (**7**).* To a suspension of **2b** (9.0 g) in H_2O (200 ml) was added a small excess of 5% $NaHCO_3$ solution, and the mixture was stirred overnight. The crystals were collected by filtration to give almost pure **7** (6.0 g, 98%); mp 170—172 °C. Recrystallization from dioxane gave a pure sample as colorless leaflets; mp 176—178 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1600, 1570, 1513. NMR (DMSO-d_6) δ: 3.31 (3H, s), 6.6—7.6 (10H, m). Found: C, 65.93; H, 4.88; N, 10.26%. Calcd for $C_{15}H_{13}ON_2Cl$: C, 66.05; H, 4.80; N, 10.27%.

*1-Methyl-4-phenylquinazolinium Bromide (**2c**).* **2c** (2.7 g, 78.0%) was prepared from **6** (4.0 g) and excess 47% HBr (8 ml) in *i*-PrOH. Recrystallization from DMF-AcOEt gave an analytical sample as pale yellow leaflets; mp 243—244 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1610, 1590, 1520. NMR (DMSO-d_6) δ: 3.81, 4.65 (3H, two singlets), 7.35—8.75 (9H, m), 8.97, 10.27 (1H, two singlets). Found: C, 59.80; H, 4.42; N, 9.07%. Calcd for $C_{15}H_{13}N_2Br$: C, 59.81; H, 4.35; N, 9.30%.

*1-Methyl-4-phenyl-6-chloroquinazolinium Bromide (**2d**).* To a suspension of **7** (5.0 g) in *i*-PrOH (50 ml) was added an excess of 25% HBr/AcOH (*ca.* 30 ml) and the mixture was warmed until it became clear. After cooling, the yellow leaflets which had precipitated were collected by filtration and washed with *i*-PrOH (5.0 g, 81.2%); mp 230—231 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1596, 1528, 1486. NMR (DMSO-d_6) δ: 3.82, 4.67 (3H, two singlets), 7.0—8.8 (8H, m), 9.06, 10.31, (1H, two singltes). Found: C, 53.45; H, 3.64; N, 8.12%. Calcd for $C_{15}H_{12}N_2BrCl$: C, 53.67; H, 3.60; N, 8.34%.

*Reactions of Quinazolinium Salts (**2a—d**) with CH_2N_2.* *1)*: To a stirred suspension of **2a** (1.05 g) in THF (100 ml) was added dropwise a freshly-prepared ethereal solution of CH_2N_2 (from 4 g of *p*-TsN(NO)CH_3) at 10 °C over a 1-hr period. After standing for 15 min, the mixture was concentrated to dryness and the residual oil was crystallized as a picrate (1.2 g, 69.4%); mp 162—164 °C. Recrystallization from a mixture of DMF and EtOH gave 1-methyl-2-iodomethyl-4-phenyl-1,2-dihydroquinazoline (**8a**) picrate as dark red prisms; mp 163—165 °C. NMR (DMSO-d_6) δ: 3.33 (3H, s), 3.45—3.75 (2H, m), 5.79 (1H, d.d, J=10 Hz, J=6 Hz), 6.8—8.0 (9H, m), 8.62 (2H, s). Found: C, 44.53; H, 3.21; N, 11.82%. Calcd for $C_{22}H_{18}O_7N_5I$: C, 44.68; H, 3.07; N, 11.84%.

2): To a stirred suspension of **2c** (0.9 g) in CH_2Cl_2 (100 ml) was added a freshly-prepared ethereal solution of CH_2N_2 (from 6.0 g of *p*-TsN(NO)CH_3) at 10 °C over a 1-hr period. After standing for 1 hr, the mixture was washed with aqueous 5% $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated to dryness. The residual oil was crystallized as a picrate (0.3 g, 28.3%), mp 130—132 °C (decomp.). A pure sample of 1-methyl-2-bromomethyl-4-phenylquinazoline (**8c**) picrate was obtained as red prisms by recrystallization from EtOH; mp 133—135 °C (decomp.). Found: C, 49.75; H, 3.52; N, 13.48%. Calcd for $C_{22}H_{18}O_6N_5Br$: C, 50.01; H, 3.43; N, 13.25%.

The mother liquor from the crystallization of the picrate was concentrated, and the residue was poured into aqueous 5% LiOH solution. The oil was extracted with benzene, and the benzene layer was dried (K_2CO_3) and concentrated to dryness. Tlc of the residual oil indicated the presence of two major products. This was chromatographed on silica gel (30 g, solvent $CHCl_3$-EtOH, 200 : 1). The first fraction (110 mg, 11.0%) was crystallized from *n*-hexane. Recrystallization from petroleum ether gave 1-methyl-3-bromomethyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**10c**) as colorless prisms, mp 81—83 °C. IR ν_{max}^{Nujol} cm^{-1}: 1614, 1595, 1580, 1563, 1492. UV λ_{max}^{EtOH} nm ($\varepsilon\times10^{-3}$): 242 (23.0), 346 (2.9). NMR ($CDCl_3$) δ: 2.79 (3H, s), 3.4—3.9 (5H, m), 6.9—7.75 (9H, m). Mass *m/e*: 330, 328 (M^+), 249 (M^+-81, M^+-79). Found: C, 61.85; H, 5.34; N, 8.53%. Calcd for $C_{17}H_{17}N_2Br$: C, 62.01; H, 5.21; N, 8.51%.

The second fraction (110 mg, 13.1%) was crystallized from petroleum ether; subsequent recrystallization from petroleum ether gave 1-methyl-3-ethoxy-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**9**) as colorless prisms; mp 90—92 °C. IR ν_{max}^{Nujol} cm^{-1}: 1603, 1595, 1564. UV λ_{max}^{EtOH} nm ($\varepsilon\times10^{-3}$): 242 (22.0), 346 (1.7). NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 2.80 (3H, s), 3.25—4.3 (4H, m), 4.73 (1H, q, J=5 Hz), 6.9—7.8 (1H, m). Mass *m/e*: 280 (M^+). Found: C, 76.89; H, 7.11; N, 9.88%. Calcd for $C_{18}H_{20}ON_2$: C, 77.11; H, 7.19; N, 9.99%.

3): The reaction of **2c** (18 g) with CH_2N_2 in CH_2Cl_2 (200 ml) was carried out at −18——20 °C to obtain **10c** picrolonate (2.7 g, 74%); mp 128—131 °C (decomp.). The crystals were dissolved in $CHCl_3$ and passed through alumina (50 g). The product was identified as **10c**.

4): 1-Methyl-3-iodomethyl-5-phenyl-7-chloro-2,3-dihydro-1*H*-1,4-benzodiazepine (**10b**, 500 mg) was obtained from **2b** (1.0 g) as colorless prisms (*i*-PrOH); mp 145—147 °C. Yield, 46.6%. IR ν_{max}^{Nujol} cm^{-1}: 1615, 1595, 1555, 1490. UV λ_{max}^{EtOH} nm ($\varepsilon\times10^{-3}$): 233 (26.0), 250 (21.0), 358 (1.2). NMR ($CDCl_3$) δ: 2.77 (3H, s), 3.2—3.9 (5H, m), 6.8—7.8 (8H, m). Mass *m/e*: 410 (M^+), 283 (M^+-127). Found: C, 49.55; H, 3.99; N, 6.72%. Calcd for $C_{17}H_{16}N_2ClI$: C, 49.72; H, 3.93; N, 6.82%.

From the mother liquor, 1-methyl-2-iodomethyl-4-phenyl-7-chloro-1,2-dihydroquinazoline (**8b**) picrate (400 mg) was obtained as dark red prisms (DMF–EtOH); mp

156—158 °C. Yield, 24.5%. NMR (DMSO-d_6) δ: 3.30 (3H, s), 3.45—3.95 (2H, m), 5.65—5.95 (1H, m), 7.0—8.0 (9H, m), 8.60 (2H, s). Found: C, 41.95; H, 2.52; N, 11.30%. Calcd for $C_{22}H_{17}O_7N_5ClI$: C, 42.23; H, 2.74; N, 11.19%.

5): 1-Methyl-3-bromomethyl-5-phenyl-7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine (**10d**, 600 mg) was obtained from **2d** (1.0 g) as colorless prisms (Et_2O-*n*-hexane); mp 140—142 °C. Yield, 55.3%. IR ν_{max}^{Nujol} cm^{-1}: 1615, 1575, 1555, 1490. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 233 (26.0), 250 (24.0), 358 (1.0). NMR ($CDCl_3$) δ: 2.78 (3H, s), 3.35—4.0 (5H, m), 6.8—7.8 (8H, m). Mass *m/e*: 364, 362 (M^+), 283 (M^+-81, M^+-79). Found: C, 55.98; H, 4.49; N, 7.68%. Calcd for $C_{17}H_{16}N_2BrCl$: C, 56.14; H, 4.43; N, 7.70%.

*Reduction of 1-Methyl-2-iodomethyl-4-phenyl-1,2-dihydroquinazoline (**8a**) with Raney Ni.* A mixture of **8a** picrate (0.5 g) and aqueous 5% LiOH solution (10 ml) was extracted with benzene and the extract was dried (K_2CO_3). The solution was hydrogenated with 2 ml of Raney Ni under 2.5 kg/cm² (30 min). The catalyst was removed by filtration and the filtrate was washed with aqueous 5% $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from EtOH as a picrate and recrystallization from EtOH gave 1,2-dimethyl-4-phenyl-1,2-dihydroquinazoline (**11**) picrate as red needles (0.2 g, 50%); mp 160—163 °C (decomp.). NMR (DMSO-d_6) δ: 1.46 (3H, d, J=6 Hz), 3.20 (3H, s), 5.61 (1H, q, J=6 Hz), 6.75—8.0 (9H, m), 8.60 (2H, s). Found: C, 56.30; H, 4.20; N, 14.78%. Calcd for $C_{22}H_{19}O_7N_5$: C, 56.77; H, 4.12; N, 15.05%.

*Reduction of 1-Methyl-3-iodomethyl-5-phenyl-7-chloro-2,3-dihydro-1H-1,4-benzodiazepine (**10b**) with Raney Ni.* A mixture of **10b** (1.8 g), KOH (300 mg), and EtOH (50 ml) was hydrogenated with 1.5 ml of Raney Ni under 2.5 kg/cm². The catalyst was removed by filtration, and the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$, and the solution was washed with H_2O, dried (K_2CO_3), and concentrated. The residue was crystallized from *n*-hexane, and the crystals were collected by filtration. Recrystallization from ether-*n*-hexane gave pure 1,3-dimethyl-5-phenyl-7-chloro-2,3-dihydro-1*H*-1,4-benzodiazepine (**12**, 0.5 g, 40.5%); mp 101—102 °C. IR ν_{max}^{Nujol} cm^{-1}: 1607, 1570, 1490. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 231 (23.9), 250 (20.3), 356 (1.1). NMR ($CDCl_3$) δ: 1.42 (3H, d, J=6 Hz), 2.75 (3H, s), 3.4—4.0 (3H, m), 6.75—7.75 (8H, m). Found: C, 71.97; H, 6.06; N, 9.77%. Calcd for $C_{17}H_{17}N_2Cl$: C, 71.69; H, 6.02; N, 9.84%. The IR spectrum of this compound was identical with that of the authentic sample.[11,12] Treatment of the mother liquor from crystallization of crude **12** with MeOH/HCl gave **12**·HCl (0.5 g, 35.5%); mp 231—232 °C. Found: C, 63.88; H, 5.67; N, 8.47%. Calcd for $C_{17}H_{18}N_2Cl_2$: C, 63.55; H, 5.65; N, 8.72%.

Reduction of 1-Methyl-3-bromomethyl-5-phenyl-7-chloro-2,3-dihydro-1H-1,4-benzodiazepine with Raney Ni. **10d** was hydrogenated in the same way, and the product was identified as **12**.

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