4-Oxo-1,2,3,4-tetrahydroquinazolines. V. Ring Expansion Reaction of 1-Methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium Bromide with Diazoalkanes

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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Reactions of 1-methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium bromide (**13**) with diazoalkanes were investigated. Treatment of **13** with diazomethane in EtOH gave a ring-expansion product **14** in a good yield. A mechanism which involves the formation of azirinoquinazolinium bromide and a subsequent SN1 type ring opening was discussed. Treatment of **13** with phenyldiazomethane also afforded benzodiazepine **16**. However, reaction of **13** with ethyldiazoacetate in the presence of $CuSO_4$ gave 4-oxo-1,2,3,4-tetrahydroquinazoline **17**.

We have recently reported[1] that 2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (**1**) undergo ring expansion on treatment with sodium ethoxide in ethanol to give 3-ethoxy-4-aryl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(*H*)-ones (**3**). The mechanism of the reaction, which involves the formation of an intermediate, azirinoquinazoline (**2**), and the subsequent ring cleavage of the aziridine moiety, was corroborated by the isolation of the intermediate. This ring-expansion reaction provided us a convenient method for the synthesis of the seven-membered analogs (**4**)[2] of 1-dialkylaminoacetyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines.[3] In connection with our studies of the structure-activity relationship between the 1-dialkylaminoacetyl-, and the 1-dialkylaminoethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines,[4] our interest was directed toward the synthesis of 1-dialkylaminoalkylbenzodiazepines (**6**). We devised a similar ring-opening reaction azirinoquinazolinium compound for the preparation of the benzodiazepine (**6**). It was envisaged that the intramolecular cyclization of 1-alkyl-2-halomethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazoline, or the addition of CH_2N_2 to 1-alkyl-3-aryl-4-oxo-quinazolinium salt, followed by the ring opening of the aziridinium moiety (**5**) with nucleophiles, might give 1-alkyl-3-substituted 4-aryl-1,4-benzodiazepin-5(*H*)-one in a single step.

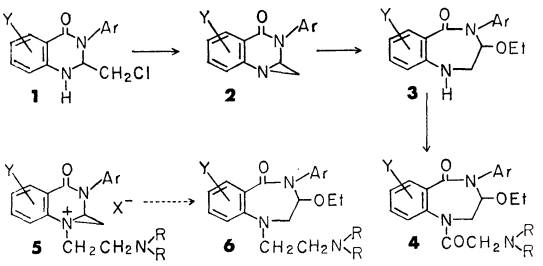

Chart 1.

A number of papers[5] dealing with quarternary aziridinium salt have appeared in the literature. Crist and Leonard[6] reported that the reaction of simple imminium perchlorates with diazomethane gave the corresponding aziridinium salts, which then underwent ring opening by a solvolysis-type reaction, by nucleophilic displacement, or by thermal rearrangement. They also investigated the interconversion of the substituted β-chloroethylamine and the aziridinium salt. Bernhard and Snieckus[7] found that treatment of 3,4-dihydro-2-methylisoquinolinium perchlorate with diazomethane afforded a mixture of aziridinium salts, which then underwent reaction with MeOH to produce the benzazepine and the benzazocine.

The preparation of the intermediates, 1-methyl-2-bromomethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline(**10**) and 1-methyl-3-phenyl-4-oxo--3,4-dihydroquinazolinium bromide (**13**), was carried out according to our previously-reported methods.[4] To prepare the azirinoquinazolinium compound, the reaction of **10** with $AgClO_4$ was attempted under the conditions[8] which had been used in the preparation of the aziridinium compound. However, neither the azirinoquinazolinium compound nor the ring enlarged product could be obtained. 2-[*N*-methyl-*N*-(1,2-diethoxyethyl)amino]benzanilide (**11**) was obtained as the only isolable product. This unexpected result is probably due to the low basicity (nucleophilicity) of the nitrogen atom at the 1-position.

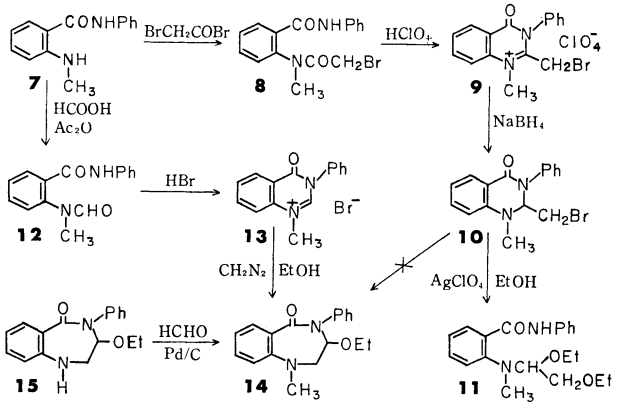

Chart 2.

The alternative method, addition of diazomethane to the quinazolinium compound **13**, was investigated. Treatment of **13** with diazomethane in EtOH at 0—5 °C gave 1-methyl-3-ethoxy-4-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(*H*)-one (**14**) in a 67.6% yield. The NMR spectrum of **14** showed the signals of an ethoxy group and an *N*-methyl group in the usual region, a multiplet at δ 3.15—3.85 which overlapped with the methylene quartet of the ethoxy group, and a triplet at δ 4.97 (J=5 Hz). The structure was confirmed by a direct comparison of its spectral data with those of an authentic sample derived from 3-ethoxy-4-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(*H*)-one (**15**)[1] by methylation. The mechanism of the reaction can be explained on the basis of Leonard's

proposal[5] regarding the ring opening of the aziridinium compound. The process for the formation of aziridinium bromide (**B**) probably involves the initial attack of diazomethane at the higher electrophilic carbimino position of the iminium bromide, and the subsequent ring closure to the aziridinium bromide (**B**), as is shown in Chart 3. It seems likely that this aziridinium bromide (**B**) is very unstable because of its highly strained structure, and that ring opening takes place spontaneously by the fission of the 1,3-bond to give carbonium ion (**C**), which may then afford a bromide (**D**). Since the presence of the nitrogen atom (at the 4-position) apparently effects the dissociation of the bromide (**D**) to the carbonium ion (**C**), the bromide (**D**) must be in equilibrium with the carbonium ion (**C**); therefore, the ethanolysis of the carbonium ion (**C**) results in the formation of **14**.

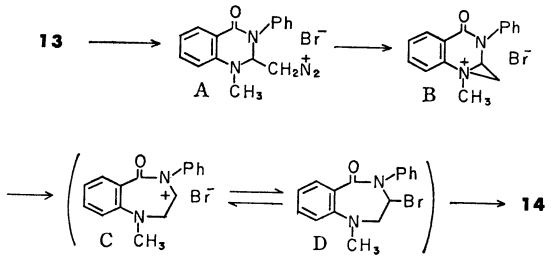

Chart 3.

Treatment of **13** with phenyldiazomethane in EtOH at room temperature afforded a product possessing the benzodiazepine ring system in a moderate yield. The structure was identified as 1-methyl-2,4-diphenyl-3-ethoxy-1,4-benzodiazepin-5(*H*)-one (**16**) on the basis of the elemental analysis and the spectral data, though the stereochemistry of compound **16** remained unclarified. The UV spectrum [maximum at 226 nm (ε 33400), 265 (sh), 334 (4300)] corresponded closely to the data for **14**. The NMR spectrum showed the signals of an ethoxy group in the usual region, a methyl singlet at δ 2.77, and an AB quartet at δ 4.85 and 5.08 (J=6 Hz) assignable to the methine protons in the seven membered ring.

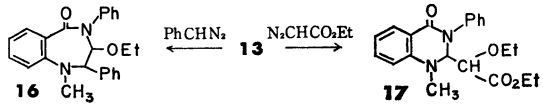

Chart 4.

Reaction of **13** with ethyl diazoacetate in EtOH did not occur even under reflux. On the other hand, reaction with ethyl diazoacetate in the presence of $CuSO_4$ at 65—70 °C gave an oily product which was shown to be homogeneous by the criteria of the glc and tlc. It has been established[9] that the $CuSO_4$-catalyzed decomposition of ethyl diazoacetate results in the formation of the carbene-copper complex, which then reacts with olefins to give cyclopropanes, but which does not undergo insertion into carbon-hydrogen bonds. Therefore, a carbene addition to the $>C=\overset{+}{N}<$ bond may be considered in the present case, though to our knowledge, no addition of a carbene at the positively-charged double bond is yet known. The planar structure of the product was shown to be 1-methyl-2-(1-ethoxy-1-ethoxycarbonylmethyl)-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**17**) by the spectral data. The mass spectrum showed a molecular ion peak (*m/e* 368) and a base peak (*m/e* 237) which must have arisen by the loss of the substituent at the 2-position. It has been reported by Bogentoft and Danielsson[10] that this type of cleavage is a main pathway in the mass fragmentation of 4-oxo-1,2,3,4-tetrahydroquinazolines. The structural assignment was also supported by the UV spectrum. The spectrum [maximum at 228 nm (ε 31000), 251 (sh), 354 (3000)] was similar to those of 4-oxo-1,2,3,4-tetrahydroquinazoline compounds and was distinctly different from those of benzodiazepines **14** and **16**. The two singlets due to the *N*-methyl groups in the NMR spectrum of **17** suggested that the product consisted of a 21 : 13 mixture of two isomers. Since no change in the signal pattern was observed at elevated temperatures, the product **17** must be a mixture of diastereoisomers. No further study on the separation of the isomers was attempted.

To evaluate the synthetic utility of this ring expansion reaction, the extension to the synthesis of the 1-dialkylaminoalkyl derivatives of 1,4-benzodiazepine is now in progress.

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.

*2-(N-methylbromoacetamido)benzanilide (**8**).* To a stirred solution of 2-(*N*-methylamino)benzanilide (**7**) (4.52 g, 0.02 mol) and pyridine (2.4 g, 0.03 mol) in benzene (120 ml) was added dropwise bromoacetylbromide (2.4 g, 0.022 mol) at room temperature, and the mixture was stirred for 1 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The chloroform layer was washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The residual oil was triturated with a mixture of *i*-Pr_2O-EtOH (1 : 1) to afford an almost pure crystalline product (5.8 g, 83%), mp 185—187 °C. An analytical sample was obtained as colorless needles by recrystallization from EtOH; mp 185—187 °C. Found: C, 55.43; H, 4.35; N, 7.72%. Calcd for $C_{16}H_{15}O_2N_2Br$: C, 55.34; H, 4.35; N, 8.07%.

*1-Methyl-2-bromomethyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium Perchlorate (**9**).* A solution of **8** (5.0 g) and an excess of 60% $HClO_4$ in EtOH was refluxed for 3 min and the precipitates were collected by filtration and washed with EtOH to give pure **9** (5.6 g, 90.3%); mp 251—253 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1723, 1625, 1594, 1563, 1490. Found: C, 44.96; H, 3.29; N, 6.30%. Calcd for $C_{16}H_{14}O_5N_2BrCl$: C, 44.72; H, 3.28; N, 6.52%.

*1-Methyl-2-bromomethyl-3-phenyl-4-oxo-1,2,3,4-tetrahedroquinazoline (**10**).* To a suspension of **9** (5.0 g, 0.012 mol) in EtOH (200 ml) was added dropwise a solution of $NaBH_4$ (0.46 g, 0.012 mol) in EtOH (20 ml) at 0—5 °C over a 1.5-hr period. The mixture was then concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$.

The chloroform layer was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was crystallized by trituration with *i*-Pr_2O and the crystals were collected by filtration to give crude **10** (3.4 g, 88.4%); mp 108—110 °C. Recrystallization from *i*-PrOH gave a pure sample as colorless prisms (3.1 g, 80.0%); mp 108—110 °C. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 229 (33.2), 252 (sh), 356 (2.9). NMR ($CDCl_3$) δ: 3.25 (3H, s), 3.53 (1H, d.d, J=11 Hz, J=5 Hz), 3.76 (1H, d.d, J=11 Hz, J=7 Hz), 5.17 (1H, d.d, J=7 Hz, J=5 Hz), 6.15—7.65 (3H, m), 7.37 (5H, s), 8.00 (1H, d.d, J=8 Hz, J=2 Hz). Found: C, 57.99; H, 4.63; N, 8.38%. Calcd for $C_{16}H_{15}ON_2Br$: C, 58.01; H, 4.56; N, 8.45%.

*Reaction of **10** with $AgClO_4$ in EtOH.* A mixture of **10** (0.5 g 0.0015 mol), $AgClO_4$ (0.31 g, 0.0015 mol), and EtOH (30 ml) was stirred at room temperature for 1.5 hr and at 50—60 °C for 8 hr. The insoluble solid that had formed was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with aqueous 5% K_2CO_3 solution, dried (K_2CO_3), and concentrated. The residual oil was chromatographed on silica gel (20 g, solvent $CHCl_3$) to give 2-[*N*-methyl-*N*-(1,2-diethoxyethyl)amino]benzanilide (**11**) as an oil (0.3 g, 58.5%). NMR ($CDCl_3$) δ: 1.08 6H, t, J=7 Hz), 2.80 (3H, s), 3.29 (2H, d, J=6 Hz), 3.49 (2H, q, J=7 Hz), 3.55 (2H, q, J=7 Hz), 4.60 (1H, t, J=6 Hz), 7.0—8.3 (9H, m), 11.25 (1H, br.s). Mass *m/e*: 324 (M^+). Found: C, 70.10; H, 7.58; N, 8.44%. Calcd for $C_{20}H_{16}N_2O_3$: C, 70.15; H, 7.65; N, 8.18%.

*2-(N-methylformamido)benzanilide (**12**).* To a mixture of formic acid (20 g) and acetic anhydride (5.0 g) was added 2-(*N*-methylamino)benzanilide (**7**, 10 g) and the reaction mixture was stirred at room temperature for 4 hr. The solution was poured into H_2O and extracted with $CHCl_3$. The chloroform layer was washed, dried (Na_2SO_4), and concentrated. The residual oil was triturated with Et_2O and the solid was collected by filtration to give almost pure **12** (10.0 g, 88.9%), mp 141—142 °C. Recrystallization from benzene gave a pure sample as colorless prisms, mp 141—142 °C. NMR ($CDCl_3$) δ: 3.12 and 3.24 (3H, two singlets in a ratio of 17 : 11), 6.9—7.75 (9H, m), 8.04 and 8.09 (1H, two singlets in the same ratio), 8.73 (1H, br.s). Found: C, 70.63; H, 5.63; N, 10.76%. Calcd for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.55; N, 11.02%.

*1-Methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium Bromide (**13**).* To a solution of **12** (10 g) in EtOH (50 ml) was added an excess of 47% HBr and the solvent was evaporated. The residue was triturated with EtOH to afford crude **13**; mp 222—223 °C (decomp.). Recrystallization from EtOH gave a pure sample (10.5 g, 84.0%); mp 225—227 °C (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1730, 1715, 1660, 1600, 1569, 1490. Found: C, 56.43; H, 4.16; N, 8.62%. Calcd for $C_{15}H_{13}ON_2Br$: C, 56.79; H, 4.13; N, 8.83%.

*1-Methyl-3-ethoxy-4-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(H)-one (**14**).* *A)*: To a solution of **13** (1.9 g, 0.006 mol) in EtOH (100 ml) was added dropwise a solution of CH_2N_2 in Et_2O (freshly prepared from 12.9 g of *p*-TsN(NO)-CH_3) at 0—5 °C during 1 hr and the mixture was stirred for 4 hr at the same temperature. After standing overnight, the solvent was evaporated and the residue was poured into aqueous K_2CO_3 solution. The oil was extracted with $CHCl_3$ and the chloroform layer was washed with H_2O, dried (K_2CO_3) and concentrated to dryness. The residue was crystallized by trituration with *i*-Pr_2O and the crystals were collected by filtration to give almost pure **14** (1.2 g, 67.6%); mp 86—88 °C. Recrystallization from *i*-Pr_2O gave a pure sample as colorless prisms; mp 89—90 °C. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 225 (24.3), 262 (sh), 352 (2.0). NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz), 2.90 (3H, s), 3.15—3.85 (4H, m), 4.97 (1H, t, J=5 Hz), 6.8—7.8 (4H, m), 7.36 (5H, s). Found: C, 72.55; H, 6.95; N, 9.38%. Calcd for $C_{18}H_{20}O_2N_2$: C, 72.95; H, 6.80; N, 9.45%.

B): A mixture of 3-ethoxy-4-phenyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(*H*)-one[1] (**15**, 5.65 g, 0.02 mol), 37% HCHO (2.5 g, 0.03 mol) and EtOH (200 ml) was warmed at 50—60 °C for 1 hr. The mixture was then hydrogenated with 5% Pd/C (2.5 g) under 2.5 kg/cm². The theoretical volume of H_2 was absorbed in 4 hr on warming. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was triturated with *i*-Pr_2O and the crystals were collected by filtration to give almost pure **14** (4.9 g, 82.4%); mp 87—88 °C. The product was identical with the sample (**14**) obtained from **13**.

*1-Methyl-2,4-diphenyl-3-ethoxy-1,2,3,4-tetrahydro-1,4-benzodiazepin-5(H)-one (**16**).* To a stirred suspension of **13** (1.0 g) was added dropwise a solution of $PhCHN_2$ in Et_2O [freshly prepared from *N*-nitroso-*N*-benzyl-*p*-toluenesulfonamide (5.8 g) by the method of Oberberger[11]] at room temperature during 1 hr. Stirring was continued overnight. The solvent was evaporated and the residue was poured into 5% aqueous K_2CO_3 solution. The oil was extracted with $CHCl_3$ and the extract was washed with H_2O, dried (K_2CO_3), and concentrated under reduced pressure. This residue was chromatographed on silica gel (100 g, solvent $CHCl_3$) to give a crystalline product **16** (350 mg, 29.8%); mp 182—184 °C (decomp.). Recrystallization from EtOH gave a pure sample colorless prisms (300 mg); mp 184—186 °C (decomp.). UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 226 (33.4), 265 (sh), 334 (4.3). NMR ($CDCl_3$) δ: 0.81 (3H, t, J=7 Hz), 2.77 (3H, s), 3.05—3.85 (2H, m), 4.85 (1H, d, J=6 Hz), 5.08 (1H, d, J=6 Hz), 6.8—7.85 (14H, m). Found: C, 77.43; H, 6.65; N, 7.69%. Calcd for $C_{23}H_{22}O_2N_2$: C, 77.39; H, 6.50; N, 7.52%.

*1-Methyl-2-(1-ethoxy-1-ethoxycarbonylmethyl)-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**17**).* To a stirred suspension of **13** (3.0 g) and $CuSO_4$ (0.6 g) in EtOH (100 ml) was added dropwise a solution of $N_2CHCOOEt$ (3.0 g) in EtOH (50 ml) at 70—75 °C during 3 hr. The insoluble solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was shown by tlc to be a mixture of a major product and three minor products. This residue was chromatographed on silica gel (180 g, solvent $CHCl_3$) to give an oil (600 mg) which was shown to be homogeneous by the criteria of the glc and tlc. IR ν_{max}^{neat} cm^{-1}: 1740, 1660, 1619, 1498. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 228 (31.0), 251 (sh), 354 (3.0). NMR (CCl_4) δ: 1.01, 1.10 (6H, two triplets in a ratio of 21 : 13, J=7 Hz), 3.06, 3.13 (3H, two singlets in the same ratio), 3.2—4.3 (5H, m), 5.24, 5.26 (1H, two doublets, J=5 Hz), 6.45—8.05 (9H, m). Mass *m/e*: 368 (M^+), 237 (base peak). Found: C, 65.62; H, 6.54; N, 7.06%. Calcd for $C_{21}H_{24}O_4N_2 \cdot H_2O$: C, 65.27; H, 6.78; N, 7.25%.

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