THERMAL RING CONTRACTION OF 3*H*-1,4-BENZODIAZEPINES INTO QUINAZOLINES

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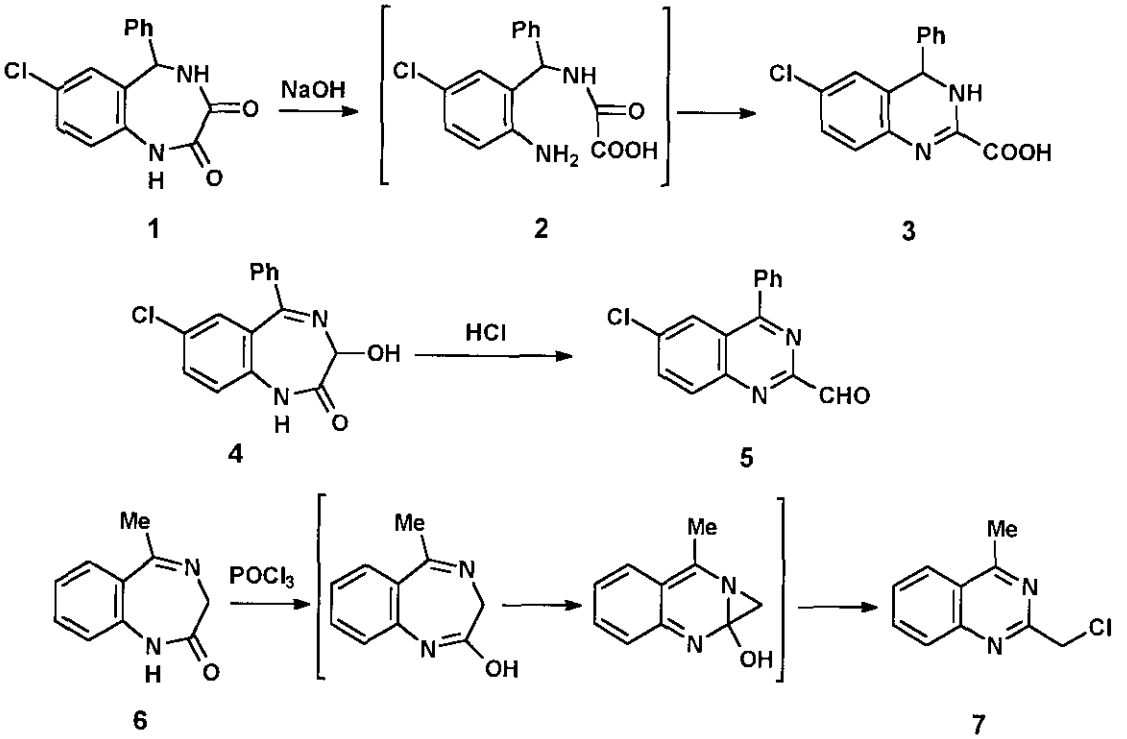
Abstract- The thermolysis of the 5-methoxy- (**11a-c**) and 5-diethylamino-3*H*-1,4-benzodiazepines (**14a-c**) resulted in a ring transformation to give the 4-methoxy- (**12a-c**) and 4-diethylaminoquinazolines (**15a-c**), respectively. The mechanism of this ring contraction is also described.

There are several reports[1] on the ring contraction of the seven-membered azaheterocyclic compounds to quinolines, isoquinolines or quinazolines. Although the chemistry of the 1,4-benzodiazepine derivatives[2] has been very widely investigated due to their biological activities among the six benzodiazepine isomers due to the isomeric positions of the two nitrogen atoms, only a few reports[3,4,5] on the contraction of the 1,4-benzodiazepines are known (Scheme 1). The base-catalyzed hydrolysis of 1,4-benzodiazepine-2,3-dione (**1**) gives the quinazoline-2-carboxylic acid (**3**) *via* α-keto carboxylic acid (**2**) as the intermediate.[3] The treatment of the 1,4-benzodiazepine derivative (**4**) with HCl affords 2-formylquinazolines (**5**).[4] Combs *et al.*[5] described a phosphoryl chloride induced ring contraction of 1,4-benzodiazepin-2-one (**6**) to 2-chloromethylquinazoline (**7**). However, no examples of the ring contractions of fully unsaturated 1,4-benzodiazepines have been reported until now.

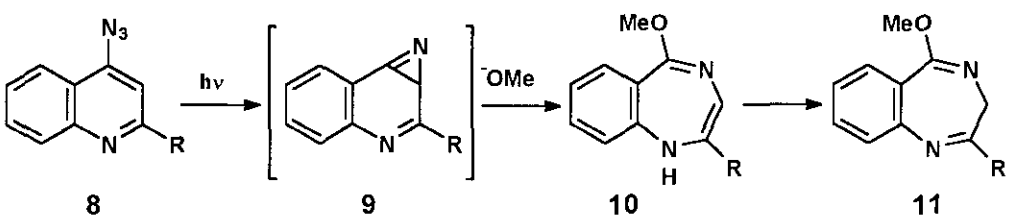
We have already succeeded in the synthesis of the fully unsaturated 1*H*- (**10**) and 3*H*-1,4-benzodiazepines (**11**)[6] by photochemical ring-expansion of 4-azidoquinolines (**8**) *via* the azirine intermediate (**9**) as shown in Scheme 2. Thus, we wish to report here the title contraction of fully unsaturated compounds.



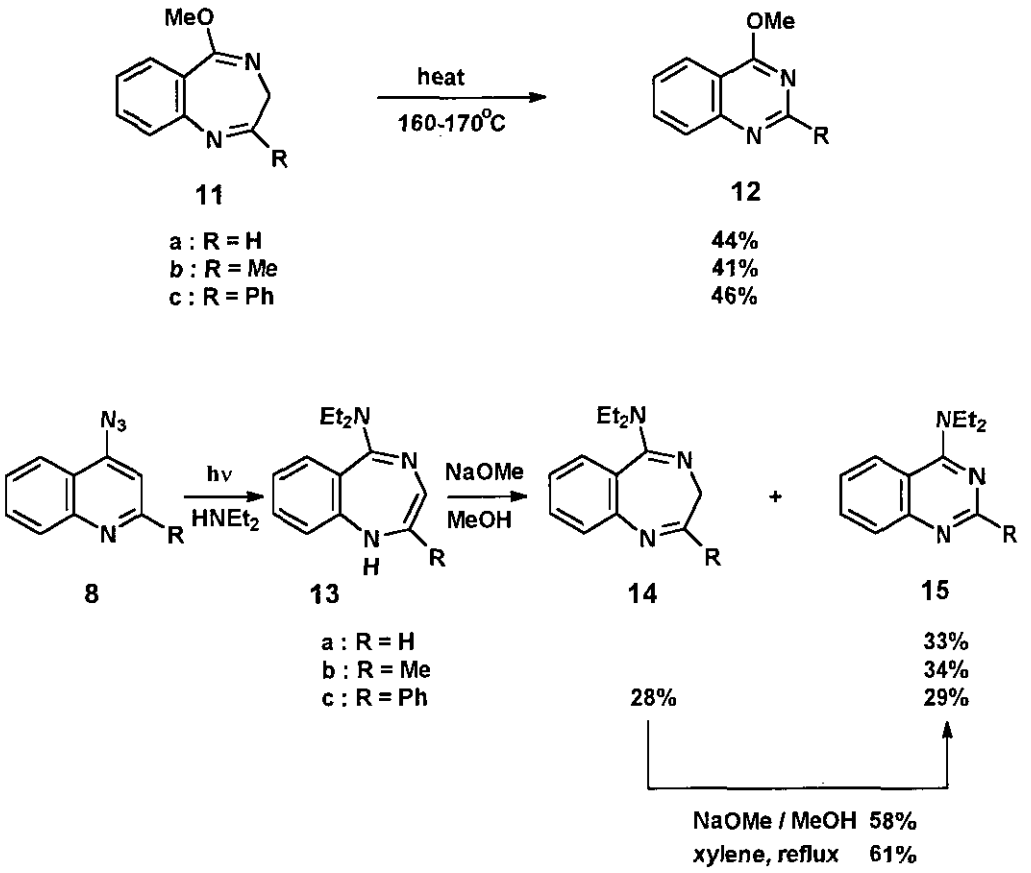
Scheme 1

The heating of 5-methoxy-3*H*-1,4-benzodiazepines (**11a-c**)[6] in diphenyl ether at 160-180 ℃ for *ca.* 6 h resulted in the formation of 4-methoxyquinazolines (**12a-c**) as characterized sole products in the yields shown in Scheme 3. All products, the 2-unsubstituted- (**12a**), 2-methyl- (**12b**) and 2-phenyl-4-methoxyquinazolines (**12c**) have been reported in the literature,[7] and are identical with authentic samples.

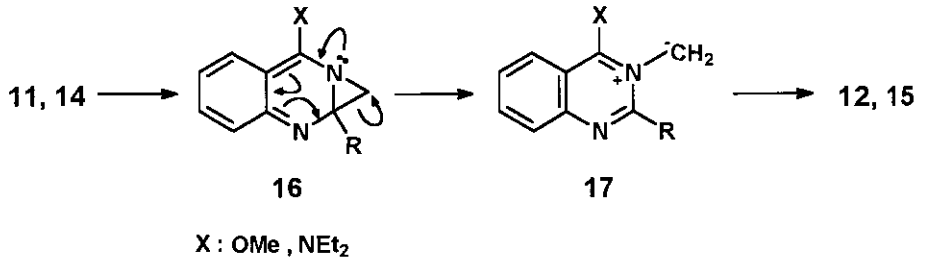
In order to examine the contraction of 5-diethylamino-3*H*-1,4-benzodiazepines (**14**), which have not previously been prepared, the 4-azidoquinolines (**8a-c**)[6] were irradiated (400 W, high-pressure Hg lamp; Pyrex filter) in dioxane in the presence of diethylamine. The resulting products, 5-diethylamino-1*H*-1,4-benzodiazepines (**13a-c**) were almost quantitatively obtained in the nearly pure state. However, these



Scheme 2



Scheme 3



Scheme 4

compounds were extremely unstable, therefor used in the following isomerization without purification. Unexpectedly, treatment of the crude 1*H*-isomers (**13a-b**) with sodium methoxide in MeOH at room temperature gave the 4-diethylaminoquinazolines (**15a**: 33 %, **15b**: 34 % yields), respectively. The required 3*H*-isomers (**14a, b**) could not be isolated. The behavior of the 2-phenyl derivative (**13c**) was

somewhat different from that of the 2-unsubstituted- (**13a**) and 2-methyl compounds (**13b**). Similar treatment of **13c** with sodium methoxide afforded a 1:1 mixture of 5-diethylamino-2-phenyl-3*H*-1,4-benzodiazepine (**14c**: 28 % yield) and 4-diethylaminoquinazoline (**15c**: 29 % yield). The 3*H*-isomer (**14c**) was converted to the quinazoline (**15c**) in *ca.* 60 % yield by further treatment with sodium methoxide or by heating in refluxing xylene. 2-Unsubstituted 4-diethylaminoquinazoline (**15a**) was identical with the authentic sample prepared from 4-chloroquinazoline and diethylamine using the reported method.[8] The other products (**15b, c**) were characterized by spectral comparison with **15a**.

A possible mechanism for this ring transformation is shown in Scheme 4. Thermal electrocyclization of 3*H*-diazepines (**11, 14**) may give the tricyclic intermediates (**16**). These aziridine compounds (**16**) may then undergo a ring-opening to give the N-ylides (**17**), which may provide the quinazolines (**12, 15**) by fission of the N-C bond.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Hitachi 270-30 spectrophotometer. MS spectra were recorded on a JEOL JMS-DX300 instrument. ^{1}H-NMR spectra were determined with a JEOL EX-90A (90 MHz) or JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as internal standard and *J* values are given in Hz. Microanalyses were performed in the Microanalytical Laboratory of this Faculty.

Thermolysis of 5-methoxy-3*H*-1,4-benzodiazepines (11a-c): Formation of 4-methoxyquinazolines (12a-c).

General Procedure: A solution of **11** (2 mmol) in diphenyl ether (10 mL) was heated for *ca.* 6 h. After cooling, the reaction mixture was chromatographed on silica gel using *n*-hexane - ether (2:1) as an eluent to give **12**. Spectral data for the reported compounds (**12a-c**) were not given in the literature, so they are reported here.

Thermolysis of **11a**: Reaction temperature: 160 ℃. 4-Methoxyquinazoline (**12a**): 44% yield, pale yellow oil, (lit.,[7] mp 35-36 ℃). MS *m/z*: 160 (M^+). ^{1}H-NMR δ: 4.14 (3H, s, 4-OMe), 7.4-8.2 (4H, m, Ph-H), 8.80 (1H, s, 2-H).

Thermolysis of **11b**: Reaction temperature: 160 ℃. 4-Methoxy-2-methylquinazoline (**12b**): 41% yield, pale

yellow oil, (lit.,[7] mp 34-35 ℃). MS *m/z*: 174 (M^+). ^{1}H-NMR δ: 2.76 (3H, s, 2-Me), 4.18 (3H, s, 4-OMe), 7.4-8.2 (4H, m, Ph-H).

Thermolysis of **11c**: Reaction temperature: 180 ℃. 4-Methoxy-2-phenylquinazoline (**12c**): 46% yield, pale yellow prisms, mp 60-62 ℃ (from *n*-hexane) (lit.,[7] mp 65-66 ℃). MS *m/z*: 236 (M^+). ^{1}H-NMR δ: 3.87 (3H, s, 4-OMe), 7.2-8.0 (9H, m, Ph-H).

Photolysis of azides (8a-c): Formation of 5-diethylamino-1*H*-1,4-benzodiazepines (13a-c)

General Procedure: A solution of **8** (5.5 mmol) and diethylamine (10 mL) in dioxane (140 mL) was irradiated with a 400 W high pressure Hg lamp for *ca.* 30 min under a nitrogen atmosphere. After removal of the solvent and excess of diethylamine *in vacuo*, the residue was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give **13** quantitatively in a nearly pure state.

13a: ^{1}H-NMR δ: 1.12 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 3.24 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 4.7 (1H, br s, 1-NH), 5.40 (1H, d, *J* = 6 Hz, 2-H or 3-H), 5.96 (1H, d, *J* = 6 Hz, 2-H or 3-H), 6.5-7.2 (4H, m, Ph-H).

13b: ^{1}H-NMR δ: 1.04 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 2.60 (3H, s, 2-Me), 3.26 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 5.36 (1H, br s, 1-NH), 6.33 (1H, s, 3-H), 6.8-7.5 (4H, m, Ph-H).

13c: ^{1}H-NMR δ: 1.00 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 3.17 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 5.0 (1H, br s, 1-NH), 6.84 (1H, s, 3-H), 7.1-8.2 (9H, m, Ph-H).

The diazepines (**13**) were unstable and decomposed during the purification. Thus, they were immediately used in the following reaction.

Treatment of 13a with NaOMe in MeOH

A solution of the crude 1*H*-isomer (**13a**: 645 mg, 3 mmol) and NaOMe (540 mg, 10 mmol) in MeOH (20 mL) was stirred at rt for 12 h, and then poured into ice-water. The aqueous mixture was extracted with ether, the extract was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica gel using *n*-hexane - ether (1:1) as an eluent to give 4-diethylaminoquinazoline (**15a**) (199 mg, 33 %) as a pale yellow oil. Spectral data for the reported compound (**15a**) were not given

in the literature,[8] so it is reported here. MS *m/z*: 201 (M^+). ^{1}H-NMR δ: 1.32 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 3.68 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 7.2-7.9 (4H, m, Ph-H), 8.60 (1H, s, 2-H).

Treatment of 13b with NaOMe in MeOH

The crude 1*H*- diazepine (**13b**: 687 mg, 3 mmol) was similarly treated with NaOMe (540 mg, 10 mmol) and worked up as described for **13a** to give 4-diethylamino-2-methylquinazoline (**15b**) (219 mg, 34 %) as a pale yellow oil. MS *m/z*: 215 (M^+). ^{1}H-NMR δ: 1.32 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 2.60 (3H, s, 2-Me), 3.66 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 7.2-7.9 (4H, m, Ph-H). *Anal.* Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.33; H, 8.16; N, 19.39.

Treatment of 13c with NaOMe in MeOH

The crude 1*H*- diazepine (**13c**: 873 mg, 3 mmol) was similarly treated NaOMe (540 mg, 10 mmol) and worked up as described for **13a** to give **14c** and **15c**.

5-Diethylamino-2-phenyl-3*H*-1,4-benzodiazepine (**14c**): 244 mg, 28 % yield, pale yellow oil. MS *m/z*: 291 (M^+). ^{1}H-NMR δ: 1.00 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 2.9-3.4 (4H, m, NCH_2CH_3 x 2), 3.25 and 4.78 (each 1H, each d, *J* = 11 Hz, 3-H_2), 7.0-7.6 and 8.0-8.2 (7H, m and 2H, m, Ph-H). *Anal.* Calcd for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26; N, 14.42. Found: C, 78.09; H, 7.24; N, 14.20.

4-Diethylamino-2-phenylquinazoline (**15c**): 241 mg, 29 % yield, yellow oil. MS *m/z*: 277 (M^+). ^{1}H-NMR δ: 1.34 (6H, t, *J* = 7 Hz, NCH_2CH_3 x 2), 3.69 (4H, q, *J* = 7 Hz, NCH_2CH_3 x 2), 7.2-8.0 and 8.4-8.6 (7H, m and 2H, m, Ph-H). *Anal.* Calcd for $C_{18}H_{19}N_3$: C, 77.94; H, 6.91; N, 15.15. Found: C, 78.19; H, 7.04; N, 15.00.

Conversion of 14c to 15c

Method A: A solution of **14c** (128 mg, 0.44 mmol) and NaOMe (1.00 g, 1.85 mmol) in MeOH (10 mL) was stirred at rt for 24 h, and then poured into ice-water. The aqueous mixture was extracted with ether, the extract was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica gel using *n*-hexane - ether (1:1) as an eluent to give **15c**: 70 mg; 58 % yield.

Method B: A solution of **14c** (116 mg, 0.4 mmol) in xylene (5 mL) was refluxed for 6 h. After cooling, the reaction solution was chromatographed on silica gel using *n*-hexane - ether (1:1) as an eluent to give **15c**: 69 mg; 61 % yield.

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