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Studies on Diazepines. XXI.[1] Photochemical Synthesis of 1*H*-2,4-Benzodiazepines from 4-Azidoisoquinolines

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Irradiation of 4-azidoisoquinolines (**1a**—**e**) in the presence of sodium methoxide resulted in ring-expansion to give 5-methoxy-1*H*-2,4-benzodiazepines (**10**): the structures of the products were confirmed by the following chemical studies as well as spectral analyses. Treatment of the diazepines (**10**) with hydrochloric acid or acidic alumina in methanol resulted in ring-contraction to afford 1-aminoisoindolenines (**14**), and treatment with acetic anhydride gave the ring-opened products (**16**). The diazepines (**10**) were also converted to 1-methoxyisoindolenines (**19**) by further irradiation and to the diazepin-3-one (**21**) by treatment with either mesitylnitrile oxide or lead tetraacetate.

Keywords——photolysis; ring-expansion; ring-contraction; nitrene; 4-azidoisoquinoline; 1*H*-2,4-benzodiazepine; isoindolenine

The synthesis of new fully unsaturated seven-membered heterocycles, heteroepines, has recently been an object of extensive study.[2] As for benzodiazepines, 1,2-,[3,4] 1,3-,[5] and 2,3-benzodiazepines[6,7] and related fused diazepines[8] condensed with aromatic heterocyclic rings such as pyridine, thiophene, furan, and pyrrole have been prepared by the photo-induced rearrangement of fused pyridine *N*-imides[3,5,7,8] or by the thermal cyclization of *o*-substituted styrene compounds.[4,6] However, the synthesis of 2,4-benzodiazepines had not been reported.

On the other hand, the singlet phenylnitrenes generated from azido-,[9] nitro-, and nitrosobenzenes[10] are known to undergo ring-expansion to give azepines *via* the azirine or the azacycloheptatetraene intermediate upon photolysis or thermolysis in the presence of bases such as alkoxides, as shown in Chart 1.

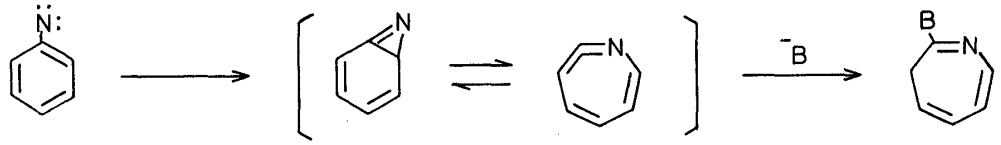


Chart 1

Therefore, as part of our continuing studies on diazepines[3,5,7,8] and on aryl azides,[11] we were interested in the photochemical behavior of 4-azidoisoquinolines under basic conditions, and we report here the formation and some reactions of 1*H*-2,4-benzodiazepines.[12] Recently, Suschitzky *et al.*[13] reported the synthesis of 5-methoxy-1*H*-2,4-benzodiazepine (**10a**) by a method similar to that described in the present work, but the data given for their compound are different from those of the diazepine (**10a**) obtained by us.

The synthetic routes to the starting 4-azidoisoquinolines used in the present reaction are shown in Chart 2. 4-Azidoisoquinoline (**1a**) prepared by the reported method[14] was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to give the *N*-oxide (**2**: 73% yield), which was treated

with phosphorus oxychloride to afford 4-azido-1-chloroisoquinoline (**1e**) in 62% yield. 4-Azido-1-methoxyisoquinoline (**1d**) was prepared in 94% yield by treatment of **1e** with sodium methoxide. Treatment of 4-bromo-1-chloroisoquinoline (**3**)[15] with methylmagnesium iodide in the presence of dichloro[1,1′-bis(diphenylphosphino)butane]palladium (II) [Pd(dppb)-Cl_2][16] as a catalyst gave the 1-methyl derivative (**4**) in 52% yield. Heating of **4** in aqueous ammonia in the presence of copper (II) sulfate resulted in the formation of the 4-amino compound (**5**: 82% yield), which gave 4-azido-1-methylisoquinoline (**1b**: 60% yield) by diazotization followed by treatment with sodium azide. Similarly, 4-azido-1-phenylisoquinoline (**1c**) was prepared from 4-bromo-1-phenylisoquinoline (**6**)[17] *via* 4-amino-1-phenylisoquinoline (**7**) in 87% yield.

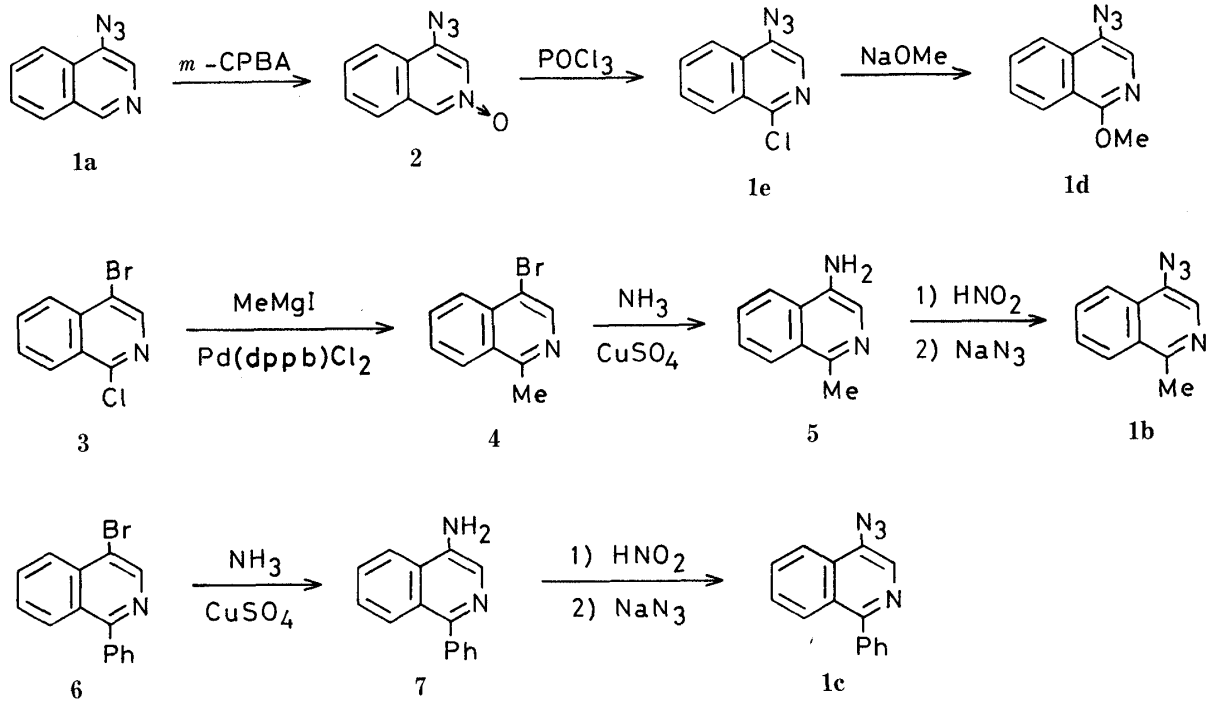
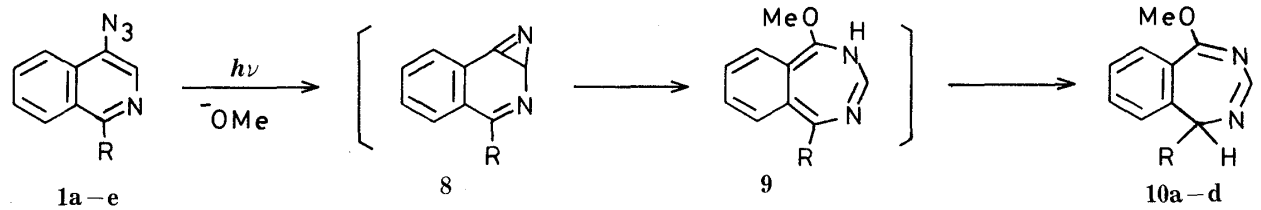


Chart 2

Irradiation of the azides (**1a—e**) in methanol–dioxane[18] (1 : 1) containing sodium methoxide for 30—40 min resulted in the formation of the desired 2,4-benzodiazepines (**10a—d**) in 45—70% yields, as the sole ring-expansion products. In the case of the 1-chloroisoquinoline (**1e**), the chlorine atom was replaced by methoxide under the present basic reaction conditions to afford the same 1-methoxydiazepine (**10d**) as that obtained from **1d**. The formation of **10** may involve ring-expansion of the azirine intermediate (**8**) derived from the initially formed singlet nitrene to the unstable anti-aromatic NH-diazepine (**9**), which tautomerizes to the more stable CH-form (**10**).



a : R = H b : R = Me c : R = Ph d : R = OMe e : R = Cl

Chart 3

These diazepines (**10**) are extremely susceptible to decomposition in a silica gel or alumina column. Thus, the photolyzed solution was evaporated and the residue was extracted with *n*-hexane to give nearly pure diazepines, which could be further purified only by Sephadex or kieselguhr chromatography. The nuclear magnetic resonance (NMR) spectral data for the diazepines (**10**), particularly for **10b** in which the 1-methyl protons (δ 1.74) are coupled to C_1-H (δ 4.1) with $J=7$ Hz, are consistent with the proposed 1*H*-structure and eliminate other possible 3*H*- and 5*H*-tautomers.

The physical and NMR spectral data for **10a** obtained by us (see Experimental) are quite different from those[19] already reported.[13] In the literature,[13] the photolyzed solution was neutralized with hydrochloric acid in methanol and then chromatographed on acidic alumina to give a product identified as the 2,4-benzodiazepine (**10a**) in 20% yield. Therefore, we examined such treatment with acids, but obtained only isoindolenine derivatives and no other compounds. Although the photolysis and treatment of the photolyzed solution were carried out under various conditions, the compound described by Suschitzky *et al.* could not be obtained.

On being passed through an acidic alumina column in methanol, the diazepines (**10a—c**) underwent ring contraction to give the 3-aminoisoindolenines (**14**) in 80—90% yields as the hydrochlorides. The salts (**14**) were also obtained by treatment of **10** with hydrochloric acid in methanol in *ca.* 80% yields. Treatment of **10a—c** with acetic anhydride at room temperature resulted in ring-opening with acetylation to give the diacetyl compounds (**16**) in 40—50% yields. On the other hand, treatment of **10a** with methanol in the presence of acetic acid instead of hydrochloric acid gave the adduct (**17**: 36% yield), which was further treated with 1% hydrochloric acid in methanol to yield the isoindolenine (**14a**) in 85% yield.

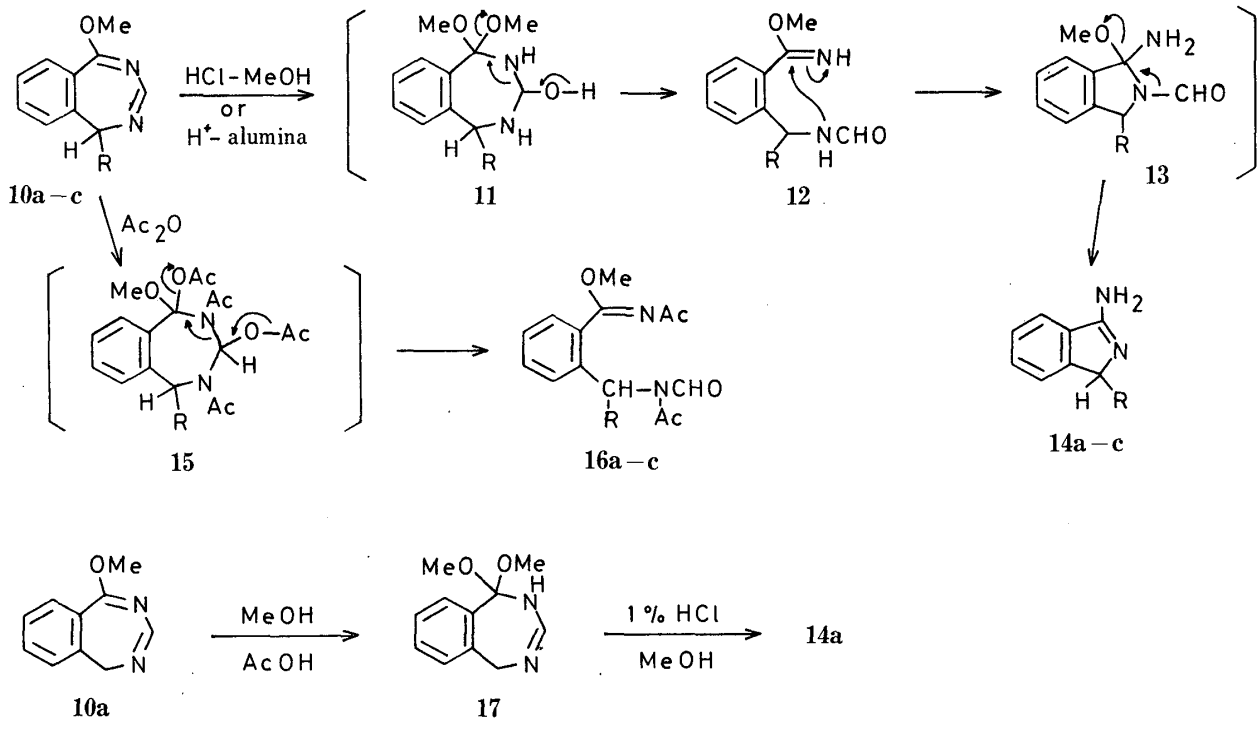


Chart 4

The above results indicate that the ring contraction of **10** to **14** may proceed by initial formation of the adduct (**11**), which undergoes ring-opening to **14** *via* the formyl intermediates (**12**) and (**13**); acidic alumina contains hydrochloric acid. The reaction with acetic anhydride may also proceed by initial formation of the adduct (**15**), which undergoes ring-opening to give the products (**16**).

Further irradiation of the diazepines (**10a—c**) in methylene chloride for 6—7 h afforded 3-methoxyisoindolenines (**19**) in 40—55% yields, presumably *via* the tricyclic intermediate (**18**); this photochemical behavior is analogous to that observed for 1*H*-1,3-,[5] and 1*H*-2,3-benzodiazepines[6,7] and supports the proposed 1*H*-2,4-benzodiazepine structure, as do the following chemical studies. Treatment of **10a** with either mesitylnitrile oxide[20] or lead tetraacetate gave the 3-oxo compound (**21**) in 30—40% yield, *via* the intermediates **20** and **22**, respectively. These results are also analogous to those for 1,2- and 1,3-benzodiazepines. Sodium borohydride reduction of **10a** afforded the 2,3-dihydrodiazepine (**23**: 90% yield), which was acetylated with acetic anhydride to give the 2-acetyl compound (**24**) in 54% yield.

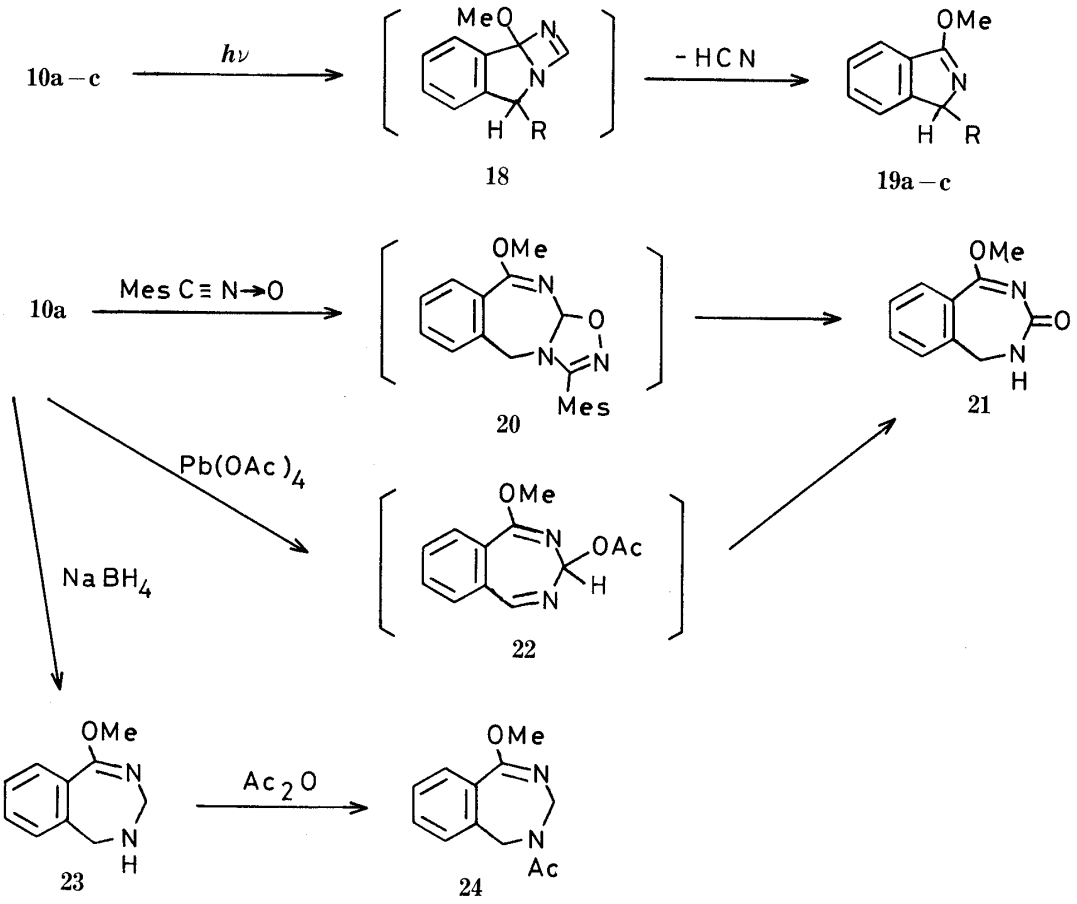


Chart 5

In conclusion, the results reported here indicate that the photo-products (**10**) obtained from 4-azidoisoquinolines (**1**) by us are 1*H*-2,4-benzodiazepine derivatives, and are the first examples of fully unsaturated 2,4-benzodiazepines.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were determined with a JASCO IRA-2 spectrometer and mass spectra (MS) were recorded on a JEOL DX-300 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard, unless otherwise stated; spectral assignments were confirmed by spin-decoupling experiments. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a JEOL FX-100 spectrometer. Microanalyses were performed in the Microanalytical Laboratory of this school by Mrs. R. Igarashi. Photolyses were carried out under a nitrogen atmosphere in an immersion apparatus equipped with a 400 W high-pressure Hg lamp and a Pyrex filter, which was cooled internally with running water.

4-Azidoisoquinoline *N*-Oxide (2)——Solid *m*-CPBA (7.5 g) was added in small portions to a solution of 4-azidoisoquinoline[14] (**1a**: 4.4 g) in CH_2Cl_2 (80 ml) with stirring in an ice bath and the mixture was allowed to stand in a

refrigerator for 20 h. The reaction solution was washed with satd. K_2CO_3, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The solid residue was recrystallized from CH_2Cl_2–isopropyl ether to give **2**: 3.5 g, 73% yield, mp 162—163 °C, pale yellow needles. MS *m/z*: 186 (M^+). ^{1}H-NMR δ: 7.40—7.60 (3H, m, 6-, 7-, and 8-H), 7.72—7.90 (1H, m, 5-H), 7.92 (1H, s, 3-H), 8.40 (1H, s, 1-H). *Anal.* Calcd for $C_6H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 57.82; H, 3.31; N, 28.28.

4-Azido-1-chloroisoquinoline (1e)——A mixture of the *N*-oxide (**2**: 3.0 g) and $POCl_3$ (50 ml) was refluxed for 2 h and concentrated *in vacuo*. Ice-water was added to the residue, and the aqueous mixture was made alkaline with Na_2CO_3 then extracted with AcOEt. The extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene–CH_2Cl_2 (1 : 1) as an eluent to give **1e**: 2.04 g, 62% yield, mp 82—83 °C, yellow prisms (from *n*-hexane–isopropyl ether). MS *m/z*: 204 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2200 ($-N_3$). ^{1}H-NMR δ: 7.64—7.80 (2H, m, 6- and 7-H), 7.92—8.06 (1H, m, 5-H), 8.06 (1H, s, 3-H), 8.12—8.30 (1H, m, 8-H). *Anal.* Calcd for $C_9H_5ClN_4$: C, 52.82; H, 2.46; N, 27.38. Found: C, 53.04; H, 2.32; N, 27.19.

4-Azido-1-methoxyisoquinoline (1d)——A solution of **1e** (2.5 g) and solid NaOMe (1.1 g) in MeOH (25 ml) was refluxed for 2 h and then evaporated *in vacuo*. Water was added to the residue and the aqueous mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to dryness *in vacuo*. The solid residue was recrystallized from isopropyl ether–*n*-hexane to give **1d**: 2.3 g, 94% yield, mp 50—51 °C, yellow needles. MS *m/z*: 200 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2200 ($-N_3$). ^{1}H-NMR δ: 4.04 (3H, s, OMe), 7.32—7.80 (3H, m, 6-, 7-, and 8-H), 7.68 (1H, s, 3-H), 7.96—8.12 (1H, m, 5-H). *Anal.* Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.61; H, 3.83; N, 27.78.

4-Bromo-1-methylisoquinoline (4)——A solution of 4-bromo-1-chloroisoquinoline[15] (**3**: 3.3 g, 0.136 mol), MeMgI (0.15 mol), and dichloro[1,4-bis(diphenylphosphino)butane]palladium (II) [Pd(dppb)Cl_2][16] (500 mg) in ether (400 ml) was refluxed for 3 d. The excess Grignard reagent was decomposed with satd. NH_4Cl and the ether layer was washed with satd. NaCl, dried, and evaporated. The residue was chromatographed on silica gel using CH_2Cl_2–acetone (50 : 1) as an eluent to give **4**: 15.63 g, 52% yield, mp 48—49 °C, colorless needles (from *n*-hexane). MS *m/z*: 221, 223 (M^+). ^{1}H-NMR δ: 2.88 (3H, s, 1-Me), 7.7—8.3 (4H, m, Ph-H), 8.76 (1H, s, 3-H). *Anal.* Calcd for $C_{10}H_8BrN$: C, 54.05; H, 3.60; N, 6.31. Found: C, 54.12; H, 3.48; N, 6.09.

4-Amino-1-methylisoquinoline (5)——A mixture of **4** (11.1 g), $CuSO_4 \cdot 5H_2O$ (2.0 g), and aq. ammonia (28%, 100 ml) was heated at 170—180 °C in an autoclave for 20 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 and the extract was washed with satd. NaCl, dried, and evaporated to dryness *in vacuo*. The residue was recrystallized from acetone–*n*-hexane to give **5**: 6.48 g, 82% yield, yellow prisms. MS *m/z*: 158 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200, 3300 (NH_2). ^{1}H-NMR δ: 2.78 (3H, s, 1-Me), 3.2—4.4 (2H, br, NH_2), 7.3—7.9 (4H, m, Ph-H), 7.72 (1H, s, 3-H). *Anal.* Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.09; H, 6.57; N, 17.75.

4-Azido-1-methylisoquinoline (1b)——A solution of $NaNO_2$ (1.87 g, 27 mmol) in water (15 ml) was added dropwise with stirring to a solution of **5** (3.95 g, 25 mmol) in aq. 15% HCl (25 ml), cooled at 0 °C in an ice-salt bath. After stirring of the mixture for an additional 1 h, a solution of NaN_3 (2.6 g, 40 mmol) in water (15 ml) was added. The reaction mixture was stirred for a further 1 h at 0 °C, then made alkaline with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with satd. NaCl, dried, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2–acetone (50 : 1) as an eluent to give **1b**: 2.76 g, 60% yield, mp 110—111 °C, yellow needles (from acetone–*n*-hexane). MS *m/z*: 184 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2100 ($-N_3$). ^{1}H-NMR δ: 2.84 (3H, s, 1-Me), 7.5—8.0 (4H, m, Ph-H), 8.11 (1H, s, 3-H). *Anal.* Calcd for $C_{10}H_8N_4$: C, 65.22; H, 4.35; N, 30.43. Found: C, 64.98; H, 4.21; N, 30.33.

4-Amino-1-phenylisoquinoline (7)——4-Bromo-1-phenylisoquinoline[17] (**6**: 14.2 g, 0.05 mol) was aminated according to the procedure described for **5** to give **7**: 9.57 g, 87% yield, mp 140—141 °C, yellow prisms. MS *m/z*: 220 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200, 3325 (NH_2). ^{1}H-NMR δ: 4.0—4.4 (2H, br, NH_2), 7.4—7.9 (9H, m, Ph-H), 8.12 (1H, s, 3-H). *Anal.* Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.78; H, 5.67; N, 12.63.

4-Azido-1-phenylisoquinoline (1c)——Compound (**7**: 5.5 g, 25 mmol) was treated as described for **5** to give **1c**: 3.87 g, 63% yield, mp 136—137 °C, yellow needles (from acetone–*n*-hexane). MS *m/z*: 246 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2150 ($-N_3$). ^{1}H-NMR δ: 7.4—7.7 and 8.0—8.2 (7H, m, and 2H, m, Ph-H), 8.44 (1H, s, 3-H). *Anal.* Calcd for $C_{15}H_{10}N_4$: C, 73.17; H, 4.06; N, 22.76. Found: C, 73.30; H, 4.01: N, 22.77.

Photolysis of the Azides (1a—e): Formation of 5-Methoxy-1*H*-2,4-benzodiazepines (10a—d)——General Procedure: A solution of **1** (0.6—1.0 g) and solid NaOMe (3—5 g) in MeOH–dioxane (1 : 1, 180 ml) was irradiated for 30—40 min. After removal of the solvent *in vacuo*, ice-water was added to the residue and the aqueous mixture was extracted with *n*-hexane. The extract was dried and evaporated *in vacuo* to give the corresponding diazepine (**10**) in a nearly pure state. The product was further purified by chromatography on Sephadex or kieselguhr using benzene as an eluent to give an analytical sample.

10a: 55% yield, mp 34—37 °C, colorless solid. MS *m/z*: 174 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (C=N). ^{1}H-NMR δ: 3.96 (3H, s, OMe), 4.26 (2H, s, 1-H_2), 7.61 (1H, s, 3-H), 7.24—7.72 (4H, m, Ph-H). ^{13}C-NMR δ: 46.8 (t, C_1), 48.4 (q, OMe), 148.8 (d, C_3), 160.4 (s, C_5), Ph-C [122.1 (d), 125.3 (s), 127.3 (d), 136.7 (s), 148.8 (d)]. *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.52; H, 4.70; N, 16.03.

10b: 67% yield, colorless viscous oil. MS *m/z*: 188 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625 (C=N). ^{1}H-NMR δ: 1.74 (3H, d, J=7 Hz, 1-Me), 4.0—4.2 (1H, m, 1-H), 4.02 (3H, s, OMe), 7.4—8.0 (5H, m, 3-H and Ph-H). *Anal.* Calcd for

$C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.15; H, 6.19; N, 14.70.

10c: 48% yield, colorless viscous oil. MS *m/z*: 250 (M^+). ^{1}H-NMR δ: 4.13 (3H, s, OMe), 5.40 (1H, s, 1-H), 6.9—8.1 (10H, m, 3-H and Ph-H). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.89; H, 5.67; N, 11.02.

10d: 45% (from **1d**) and 38% (from **1e**) yields. MS *m/z*: 204 (M^+). ^{1}H-NMR δ: 3.60 (3H, s, 1-OMe), 3.96 (3H, s, 5-OMe), 5.00 (1H, s, 1-H), 7.2—7.8 (5H, m, 3- and Ph-H). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.54; H, 5.70; N, 13.39.

Treatment of 10a—c with Acidic Alumina——General Procedure: A solution of **10** (*ca.* 1 mmol) in MeOH–CH_2Cl_2 (1 : 5) was passed through an active acidic alumina column (Merck 1078). The eluate was evaporated *in vacuo* and the residue was recrystallized from MeOH–ether to give the HCl salt of the corresponding 3-aminoisoindolenine (**14**) in 80—90% yield. A solution of the salt in MeOH was treated with ion exchange resin (Dowex 1 × 2, OH^--type) and evaporated *in vacuo*. The residue was recrystallized from MeOH–isopropyl ether to give the free base (**14**) in *ca.* 90% yield. The hygroscopic free base (**14**) was relatively unstable and gradually decomposed during purification. Thus the physical and spectral data of both salts and free bases are shown.

14a: (HCl salt) mp 210—220 °C (dec.), colorless needles. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 4.80 (2H, s, 1-H_2), 5.00 (2H, br, NH_2), 7.6—8.4 (4H, m, Ph-H). ^{13}C-NMR (CD_3OD) δ: 52.1 (t, C_1), 165.3 (s, C_3), Ph-C [124.6 (d), 124.7 (d), 128.7 (s), 129.6 (d), 134.8 (d), 145.1 (s)]. *Anal.* Calcd for $C_8H_9ClN_2$: C, 56.98; H, 5.38; N, 16.62. Found: C, 56.76; H, 5.21; N, 16.49. (Free base) mp 109—112 °C (dec.) (lit.[21] mp 112—113 °C), colorless prisms. MS *m/z*: 132 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 3200 (NH_2). ^{1}H-NMR δ: 4.43 (2H, s, 1-H_2), 6.3 (2H, br, NH_2), 7.0—7.5 (4H, m, Ph-H).

14b: (HCl salt) mp 206—207 °C (dec.), colorless needles. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.68 (3H, d, J=7 Hz, 1-Me), 4.20 (2H, s, NH_2), 5.24 (1H, q, J=7 Hz, 1-H), 7.8—8.7 (4H, m, Ph-H). *Anal.* Calcd for $C_9H_{11}ClN_2$: C, 59.17; H, 5.48; N, 15.34. Found: C, 58.92; H, 5.81; N, 15.27. (Free base) mp 94—97 °C (dec.), colorless prisms. MS *m/z*: 146 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 3200 (NH_2). ^{1}H-NMR δ: 1.44 (3H, d, J=7 Hz, 1-Me), 4.80 (1H, q, J=7 Hz, 1-H), 6.3 (2H, br, NH_2), 7.5—7.9 (4H, m, Ph-H).

14c: (HCl salt) mp 205—215 °C (dec.), colorless needles. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 4.2—5.2 (2H, br, NH_2), 5.91 (1H, s, 1-H), 7.2—7.7 (9H, m, Ph-H). *Anal.* Calcd for $C_{14}H_{13}ClN_2$: C, 68.71; H, 4.91; N, 11.45. Found: C, 68.73; H, 5.16; N, 11.28 (Free base) mp >140 °C (gradually decomposed), colorless prisms. MS *m/z*: 208 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3300, 3200 (NH_2). ^{1}H-NMR δ: 4.9 (2H, br, NH_2), 5.60 (1H, s, 1-H), 7.1—7.5 (9H, m, Ph-H).

Treatment of 10a—c with HCl in MeOH——A mixture of **10** (80—100 mg), conc. HCl (0.2 ml), and MeOH (10 ml) was stirred for 10 h at room temperature and evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH–ether to give the HCl salt of **14a—c** in *ca.* 80% yield. These salts were identical corresponding with those obtained from **10a—c** by treatment with acidic alumina.

Treatment of 10a—c with Ac_2O——General Procedure: A mixture of **10** (180—200 mg) and Ac_2O (5 ml) was stirred at room temperature overnight and poured into ice-water. The aqueous mixture was made alkaline with $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with satd. NaCl, dried, and concentrated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2–acetone (50 : 1) as an eluent to give the corresponding methyl *o*-(*N*-acetyl-*N*-formylaminomethyl)benzo-*N*-acetylimidate (**16**).

16a: 43% yield, mp 106—108 °C, colorless prisms (from isopropyl ether–*n*-hexane). MS *m/z*: 276 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1690, 1660, 1640 (C=O). ^{1}H-NMR δ: 2.12 (3H, s, Ac), 2.49 (3H, s, Ac), 4.06 (3H, s, OMe), 5.16 (2H, s, Ph-CH_2-N), 7.4—7.8 (4H, m, Ph-H), 9.65 (1H, s, NCHO). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.87; H, 5.80; N, 10.14. Found: C, 60.90; H, 5.77; N, 10.42.

16b: 40% yield, colorless viscous oil. MS *m/z*: 290 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1660, 1640 (C=O). ^{1}H-NMR δ: 1.76 (3H, d, J=8 Hz, >CHCH_3), 2.16 (3H, s, Ac), 2.46 (3H, s, Ac), 3.92 (3H, s, OMe), 6.26 (1H, q, J=8 Hz, >CHCH$_3$), 7.3—7.9 (4H, m, Ph-H), 9.25 (1H, s, NCHO). ^{13}C-NMR δ: 16.3 (q, C–CH$_3$), 23.5 (q, Ac–CH$_3$), 26.9 (q, Ac–CH$_3$), 46.5 (d, CHMe), 55.0 (q, OCH$_3$), 160.7 (s, C=N–), 163.5 (d, CHO), 171.5 (s, C=O), 182.7 (s, C=O), Ph-C [126.8 (d), 127.6 (d), 129.6 (d), 129.8 (d), 132.7 (s), 137.3 (s)]. *Anal.* Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.83; H, 6.31; N, 9.55.

16c: 56% yield, mp 95—96 °C, colorless prisms (from isopropyl ether–*n*-hexane). MS *m/z*: 352 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1690, 1670, 1650 (C=O). ^{1}H-NMR δ: 2.06 (3H, s, Ac), 2.41 (3H, s, Ac), 3.72 (3H, s, OMe), 7.0—7.6 (10H, m, Ph-CH and Ph-H), 8.89 (1H, s, NCHO). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.18; H, 5.68; N, 7.95. Found: C, 68.12; H, 5.68; N, 7.91.

Treatment of 10a with AcOH in MeOH——A mixture of **10a** (140 mg), AcOH (0.2 ml), and MeOH (20 ml) was stirred for 20 h in an ice bath. After removal of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 (30 ml). The solution was washed with satd. Na_2CO_3 and water, then dried, and concentrated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 as an eluent to give 5,5-dimethoxy-4,5-dihydro-1*H*-2,4-benzodiazepine (**17**): 60 mg, 36% yield, colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1630 (C=N). ^{1}H-NMR δ: 3.42 (6H, s, 2 × OMe), 4.50 (2H, s, 1-H_2), 4.72 (1H, s, NH), 6.16 (1H, s, 3-H), 7.36—7.80 (4H, m, Ph-H). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.73; H, 6.85; N, 13.40.

Treatment of 17 with HCl in MeOH——A mixture of **17** (39 mg), conc. HCl (0.1 ml), and MeOH (10 ml) was stirred for 12 h at room temperature and evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH–

ether to give **14a** (HCl salt): 30 mg, 85% yield. This compound was identical with the product (**14a**) obtained from **10a** by treatment with acidic alumina.

Photolysis of 10a—c——General Procedure: A solution of **10** (200—300 mg) in CH_2Cl_2 (150 ml) was irradiated for *ca.* 6 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel using CH_2Cl_2–acetone (25 : 1) as an eluent to give the corresponding 3-methoxyisoindolenine (**19**).

19a: 45% yield, colorless viscous oil. MS *m/z*: 147 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625 (C=N). ^{1}H-NMR δ: 4.08 (3H, s, OMe), 4.60 (2H, s, 1-H_2), 7.28—7.70 (4H, m, Ph-H). *Anal.* Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.39; H, 6.18; N, 9.31.

19b: 40% yield, colorless viscous oil. MS *m/z*: 161 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 (C=N). ^{1}H-NMR δ: 1.52 (3H, d, J=8 Hz, 1-Me), 4.22 (3H, s, OMe), 4.90 (1H, q, J=8 Hz, 1-H), 7.6—7.9 (4H, m, Ph-H). *Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.70; H, 6.81; N, 8.48.

19c: 56% yield, mp 111—113 °C, colorless prisms (from *n*-hexane). MS *m/z*: 223 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1620 (C=N). ^{1}H-NMR δ: 4.12 (3H, s, OMe), 5.69 (1H, s, 1-H), 7.2—7.9 (9H, m, Ph-H). *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.69; H, 5.83; N, 6.30.

Treatment of 10a with Mesitylnitrile Oxide——A mixture of **10a** (150 mg), mesitylnitrile oxide (410 mg), and benzene (20 ml) was stirred for 2 d at room temperature. After removal of the solvent *in vacuo*, the residue was chromatographed on alumina using CH_2Cl_2–acetone (10 : 1) as an eluent to give 5-methoxy-1,2-dihydro-2,4-benzodiazepin-3-one (**21**): 55 mg, 34% yield, mp 220—221 °C, colorless prisms (from CH_2Cl_2–benzene). MS *m/z*: 190 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1670 (C=O), 1640 (C=N). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 4.0 (3H, s, OMe), 4.10 (2H, s, 1-H_2), 7.1—7.7 (4H, m, Ph-H). *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.09; H, 4.99; N, 14.64.

Treatment of 10a with Lead Tetraacetate——A solution of $Pb(OAc)_4$ (300 mg) in CH_2Cl_2 (5 ml) was added dropwise with stirring to a solution of **10a** (90 mg) in CH_2Cl_2 (8 ml), cooled in an ice bath. After stirring of the mixture for an additional 3.5 h at room temperature, the excess reagent was decomposed with water. The CH_2Cl_2 layer was dried and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2–acetone (10 : 1) as an eluent to give **21** (32 mg, 30% yield), which was identical with the product obtained from **10a** by treatment with mesitylnitrile oxide.

Reduction of 10a with $NaBH_4$——Solid $NaBH_4$ (400 mg) was added in small portions to a solution of **10a** (103 mg) in MeOH (10 ml) with stirring in an ice bath. The reaction solution was stirred for an additional 10 h at room temperature and concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with satd. NaCl, dried, and evaporated to dryness *in vacuo*. The solid residue was recrystallized from *n*-hexane–isopropyl ether to give 5-methoxy-2,3-dihydro-1*H*-2,4-benzodiazepine (**23**): 93 mg, 89% yield, mp 97—98 °C, colorless needles. MS *m/z*: 176 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1640 (C=O). ^{1}H-NMR δ: 2.70 (1H, br, NH), 3.84 (2H, s, 3-H_2), 3.86 (3H, s, OMe), 4.12 (2H, s, 1-H_2), 7.12—7.60 (4H, m, Ph-H). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.82; N, 15.91. Found: C, 67.95; H, 7.18; N, 15.42.

Acetylation of 23 with Ac_2O——A mixture of **23** (180 mg) and Ac_2O (5 ml) was stirred for 20 h at room temperature and then poured into ice-water. The aqueous mixture was made alkaline with Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried and concentrated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2–acetone (50 : 1) as an eluent to give 2-acetyl-5-methoxy-2,3-dihydro-1*H*-2,4-benzodiazepine (**24**): 120 mg, 54% yield, colorless oil. MS *m/z*: 218 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (C=O). ^{1}H-NMR δ: 2.20 (3H, s, Ac), 3.80 (3H, s, OMe), 4.45 (2H, s, 3-H_2), 4.6 (2H, s, 1-H_2), 7.10—7.60 (4H, m, Ph-H). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. found: C, 65.92; H, 6.45; N, 12.99.

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