

## Photolysis of Quinoyl and Isoquinoyl Azides in the Presence of Methoxide Ions. Synthesis of Benzodiazepines and Pyridoazepines

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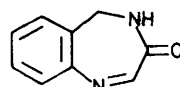
Photolysis of the title compounds in the presence of methoxide provides a convenient preparation of the corresponding methoxy-substituted bicyclic azepines and benzodiazepines in one step from readily available starting materials. Moreover, the methoxy-group in the azepines is replaceable by amines.

EXTENSIVE studies<sup>1,2</sup> have shown that photolysis of bicyclic aromatic azides in the presence of amines as a synthetic route to bicyclic azepines is limited by the position of the azido-group and the nature of the amine. We now report that quinoyl and isoquinoyl azides readily undergo ring expansion to bicyclic azepines and benzazepines on photolysis in the presence of methoxide in fair to good yields.<sup>3</sup> The position of the azido-group in the starting azide imposes no limitation on the ring expansion. Photolyses were carried out under similar conditions to those reported by Rigaudy<sup>4</sup> and his co-workers for the successful ring expansion of  $\beta$ -naphthyl and  $\beta$ -anthracenyl azides. The mechanism of these reactions has been discussed recently.<sup>5</sup>

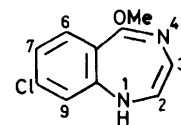
Structures of the products (1)–(11) were assigned from spectroscopic data. For instance, photolysis of 7-chloro-4-quinoyl azide in potassium methoxide-methanol-dioxan yielded 8-chloro-5-methoxy-1*H*-1,4-benzodiazepine (2) (20%) and 8-chloro-1*H*-1,4-benzodiazepin-5-one (3) (20%). The former had i.r. absorptions at 3 150 (NH) and 1 605  $\text{cm}^{-1}$  (C=N) and showed a signal in the <sup>1</sup>H n.m.r. at  $\delta$  4.0 (MeO). The aromatic region contains a doublet of doublets at  $\delta$  7.9 (7-H) and doublets at  $\delta$  8.1 (6-H) and 8.3 (7-H), the protons in the azepine ring appear at  $\delta$  6.6 and  $\delta$  7.4 (2-H and 3-H respectively). The exchangeable proton at  $\delta$  7.2 was assigned to N-1 rather than N-4 by reference to the <sup>13</sup>C n.m.r. spectrum [C-2, 127 Hz (d), C-3, 99.9 (d), and C-5, 119.3 (s)].

Certain monocyclic azides have been found to undergo ring expansion on photolysis in methanol in the absence of strong base.<sup>6</sup> However, photolysis of the bicyclic 7-chloro-4-quinoyl azide in methanol-tetrahydrofuran (1:1) merely gave 4-azo-7-chloroquinoline (triplet-derived product<sup>1</sup>), and no products attributable to ring expansion.

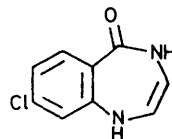
7-Methoxy-5*H*-pyrido[3,2-*c*]azepine (5) on treatment with various amines (aniline, diethylamine, and cyclohexylamine) at reflux undergoes nucleophilic substitution to give a good yield of the corresponding aminoazepines that are not available directly by photolysis of



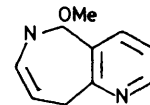
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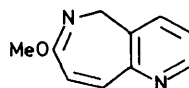
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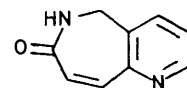
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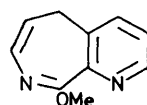
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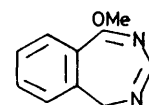
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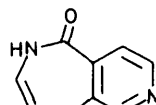
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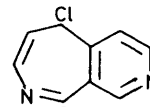
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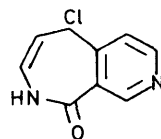
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(9)



(10)



(11)

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6-quinolyl azide in the appropriate amine. This methoxy-azepine (5) can also be converted into the azepinone (6) on heating in water-dioxan (1:1) at reflux.

Photolysis products of quinolyl and isoquinolyl azides in the presence of methoxide

Azide	Methoxyazepine or diazepine (%)	Azepinone or diazepinone (%)	Amino-(iso)quinoline (%)
3-Quinolyl-	—	(1), 43	3-, (24)
7-Chloro-4-	(2), 20	(3), 20	a
5-Quinolyl-	(4), 60	—	5-, (15)
6-Quinolyl-	(5), 64	(6), 11	6-, (10)
8-Quinolyl-	(7), 80	—	8-, (3)
4-Isoquinolyl-	(8), 20	—	a
5-Isoquinolyl-	—	(9), 21	a
5-Chloro-8-	(10), 23	(11), 18	a

\* Not determined.

## EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 instrument and <sup>1</sup>H n.m.r. spectra on a Varian EM 360 or Perkin-Elmer R32 using tetramethylsilane as internal standard. Low-resolution mass spectra were recorded on an AEI MS12.

Light petroleum refers to the fraction of b.p. 60–80 °C. Yields quoted are based on starting material consumed.

**Azides.**—7-Chloro-4-quinolyl azide was prepared by treating 4,7-dichloroquinoline with sodium azide. The rest were prepared by the diazotisation of the corresponding amine followed by treatment with sodium azide. All are known compounds, and their physical properties are in agreement with those reported in the literature.

**Photolysis of Azides: General Procedure.**—A solution of the azide (5 mmol) in potassium methoxide (3M) in methanol (40 ml) and dioxan (or TMEDA) (40 ml) was irradiated (125 W medium-pressure mercury lamp) in a Pyrex (or quartz) apparatus for at least 6 h. The photolysed solution was left at room temperature for 24 h and then neutralised with 4M-hydrochloric acid in methanol. The solvent was removed and the residue chromatographed on alumina (type H, supplied by B.D.H. Ltd.). Photolysis and chromatographic conditions are indicated thus: (co-solvent, time, apparatus, and eluant).

**Photolysis of 3-quinolyl azide.** Conditions: dioxan, 16 h, quartz, toluene; yields the 1,4-benzodiazepinone (1) (0.34 g, 43%) and 3-aminoquinoline (24%). Spectroscopic data have been reported.<sup>3</sup>

**Photolysis of 7-chloro-4-quinolyl azide.** Conditions: (a) dioxan, 16 h, quartz, toluene; 8-chloro-5-methoxy-1H-1,4-benzodiazepine (2) (0.2 g, 20%), m.p. 115 °C;  $\nu_{\max}$  (Nujol) 3 150 (NH) and 1 605 cm<sup>-1</sup> (C=N) (Found: C, 57.7; H, 4.2; N, 13.5. C<sub>10</sub>H<sub>9</sub>ClN<sub>2</sub>O requires C, 57.6; H, 4.3; N, 13.4%);  $\delta$ (CDCl<sub>3</sub>) 4.0 (3 H, s, OCH<sub>3</sub>), 6.6 (1 H, d of d, 2-H), 7.2br (1 H, NH exch. with D<sub>2</sub>O), 7.4 (1 H, d, 3-H), 7.9 (1 H, d of d, 7-H), 8.1 (1 H, d, 6-H), and 8.3 (1 H, d, 9-H); <sup>13</sup>C  $\delta$ (CDCl<sub>3</sub>) 55.3 (q, CH<sub>3</sub>), 99.9 (d, C-3), 119.3 (s, C-5), 123.0 (d, C-7), 126.0 (d, C-9), 127.0 (d, C-2), 135.0 (s, C-5a), 149.0 (s, C-9a), 152.0 (d, C-6), and 161.8 (s, C-8). Further elution gave 3-amino-7-chloro-4-methoxyquinoline (trace), m.p. 107 °C;  $\nu_{\max}$  (Nujol) 3 400 (NH) and 1 605 cm<sup>-1</sup> (C=N);  $\delta$ (CDCl<sub>3</sub>) 4.0 (3 H, s, OCH<sub>3</sub>), 4.8br (2 H, NH<sub>2</sub> exch. with D<sub>2</sub>O), 7.4 (1 H, d of d, 6-H), 7.6 (1 H, d, 5-H), 7.9 (1 H, d, 8-H), and 8.4 (1 H, s, 2-H). Elution with toluene-chloroform (4:1) gave 8-chloro-1H-1,4-benzodiazepin-5-one (3) (0.2 g, 20%),

m.p. 144–146 °C;  $\nu_{\max}$  (Nujol) 3 150 (NH), 1 645 (C=O), and 1 605 cm<sup>-1</sup> (C=N) (Found: C, 55.8; H, 3.5; N, 14.4. C<sub>9</sub>H<sub>7</sub>ClN<sub>2</sub>O requires C, 55.5; H, 3.6; N, 14.4%);  $\delta$ (CDCl<sub>3</sub>) 5.2br (1 H, NH exch. with D<sub>2</sub>O), 6.8 (1 H, d of d, 2-H), 7.1br (1 H, NH exch. with D<sub>2</sub>O), 7.2 (1 H, d of d, 3-H), 7.8 (1 H, d of d, 7-H), 8.0 (1 H, d, 6-H), and 8.3 (1 H, d, 9-H).

Conditions: (b) TMEDA, 16 h, quartz, toluene; 8-chloro-5-methoxy-1H-1,4-benzodiazepine (0.51 g, 50%), m.p. 115 °C. Identical with compound (2). Elution with toluene-chloroform (4:1) gave 8-chloro-1H-1,4-benzodiazepin-5-one (0.21 g, 20%), m.p. 144–145 °C; identical with compound (3).

**Photolysis of 5-quinolyl azide.** Conditions: dioxan, 6 h, Pyrex, toluene; 5-methoxy-9H-pyrido[3,2-c]azepine (4) (0.49 g, 60%), b.p. 102/0.2 mmHg (Found: C, 68.7; H, 5.9; N, 15.9. C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O requires C, 68.95; H, 5.8; N, 16.1%);  $\nu_{\max}$  (Nujol) 1 605 cm<sup>-1</sup> (C=N);  $\delta$ (CDCl<sub>3</sub>) 8.6 (1 H, dd, 2-H), 7.2 (1 H, dd, 3-H), 7.95 (1 H, dd, 4-H), 6.6 (1 H, d, 7-H), 5.3 (1 H, q, 8-H), 3.9 (3 H, s, OCH<sub>3</sub>), and 3.3 (2 H, d, CH<sub>2</sub>); *m/e* 174 (M<sup>+</sup>).

**Photolysis of 6-quinolyl azide.** Conditions: dioxan, 6 h, Pyrex, toluene; 7-methoxy-5H-pyrido[3,2-c]azepine (5) (0.523 g, 64%), white crystals, m.p. 61–62 °C [light petroleum (b.p. 40–60 °C)] (Found: C, 68.85; H, 5.8; N, 16.0. C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O requires C, 68.95; H, 5.8; N, 16.1);  $\nu_{\max}$  (Nujol) 1 640 cm<sup>-1</sup> (C=N);  $\delta$ (CDCl<sub>3</sub>) 8.55 (1 H, dd, 2-H), 7.65 (1 H, dd, 4-H), 7.25 (1 H, dd, J<sub>3-4</sub> 8 Hz, 3-H), 7.38 (1 H, d, 9-H), 6.52 (1 H, d, 8-H), 4.24 (2 H, s, CH<sub>2</sub>), and 3.65 (3 H, s, OCH<sub>3</sub>); *m/e* 174 (M<sup>+</sup>). Further elution with toluene-ethyl acetate (2:1) gave 5H-pyrido[3,2-c]azepin-7(6H)-one (6) (0.082 g, 11%) (Found: C, 67.5; H, 5.1; N, 17.5. C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O requires C, 67.5; H, 5.0; N, 17.5%), white plates, m.p. 164 °C [light petroleum (b.p. 60–80 °C)-ethyl acetate 1:1];  $\nu_{\max}$  (Nujol) 3 160 (NH) and 1 660 cm<sup>-1</sup> (C=O);  $\delta$ (CDCl<sub>3</sub>) 8.64 (1 H, dd, 2-H), 7.6 (1 H, dd, 4-H), 7.25 (1 H, dd, 3-H), 7.33 (1 H, d, 9-H), 6.5 (1 H, dd, 8-H), 8.1 (1 H, b.s. exchanges with D<sub>2</sub>O, NH), and 4.17 (2 H, d, CH<sub>2</sub>); 160 (M<sup>+</sup>). Further elution with ethyl acetate-methanol (1:1 v/v) gave tars 0.17 g.

**Photolysis of 8-quinolyl azide.** Conditions: dioxan, 6 h, Pyrex, toluene; 9-methoxy-5H-pyrido[2,3-c]azepine (7) (0.59 g, 72%), white crystals, [light petroleum (b.p. 40–60 °C)], m.p. 98–99 °C (Found: C, 68.7; H, 5.7; N, 16.4. C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O requires C, 68.95; H, 5.8; N, 16.1);  $\nu_{\max}$  (Nujol) 1 605 cm<sup>-1</sup> (C=N);  $\delta$ (CDCl<sub>3</sub>) 8.6 (1 H, dd, 2-H), 7.39 (1 H, dd, 3-H), 7.6 (1 H, dd, 4-H), 6.65 (1 H, d, 7-H), 5.37 (1 H, q, 6-H), 4.0 (3 H, s, OCH<sub>3</sub>), and 2.97 (2 H, d, CH<sub>2</sub>); *m/e* 174 (M<sup>+</sup>). Further elution with methanol gave tars (0.2 g).

**Photolysis of 4-isoquinolyl azide.** Conditions: dioxan, 6 h, quartz, toluene; 5-methoxy-1H-2,4-benzodiazepine (8) (0.2 g, 20%), m.p. 72 °C (Found: C, 68.7; H, 5.6; N, 16.1. C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O requires C, 68.9; H, 5.7; N, 16.1%);  $\delta$ (CDCl<sub>3</sub>) 3.4 (3 H, s, CH<sub>3</sub>), 5.4 (2 H, s, CH<sub>2</sub>), 7.0–7.4 (4 H, m, ArH), and 8.4 (1 H, s, 3-H); *m/e* 173 (M<sup>+</sup>).

**Photolysis of 5-isoquinolyl azide.** Conditions: dioxan, 16 h, quartz, toluene-chloroform (9:1); 9H-Pyrido[4,3-c]-azepin-5-one (9) (0.2 g, 21%), m.p. 141 °C (Found: C, 67.2; H, 5.0; N, 17.3. C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O requires C, 67.5; H, 5.0; N, 17.5%);  $\nu_{\max}$  (Nujol) 3 150 (NH) 1 640 (C=O), and 1 605 cm<sup>-1</sup> (C=N);  $\delta$ (CDCl<sub>3</sub>) 3.8 (2 H, d, CH<sub>2</sub>), 5.0 (1 H, q, 8-H), 6.0br (1 H exchanges with D<sub>2</sub>O, NH), 6.6 (1 H, t, 7-H), 7.4 (1 H, d, 4-H), 8.6 (1 H, d, 3-H), and 9.6 (1 H, s, 1-H).

**Photolysis of 5-chloro-8-isoquinolyl azide.** Conditions: dioxan, 16 h, quartz, toluene; 5-chloro-9-methoxy-5H-pyrido[3,4-c]azepine (10) (0.25 g, 23%), m.p. 120–121 °C

(Found: C, 57.4; H, 4.2; N, 13.2.  $C_{10}H_9ClN_2O$  requires C, 57.6; H, 4.2; N, 13.4%);  $\delta(CDCl_3)$  3.6 (3 H, s,  $OCH_3$ ), 4.0 (1 H, d, 5-H), 5.6 (1 H, q, 6-H), 7.0 (1 H, d, 7-H), 7.4 (1 H, d, 4-H), 8.2 (1 H, d, 3-H), and 8.6 (1 H, s, 1-H).

Elution with toluene-chloroform (9 : 1) gave 5-chloro-5H-pyrido[3,4-c]azepin-9-one (11) (0.2 g, 18%), m.p. 140 °C;  $\nu_{max}$  (Nujol) 3 150 (NH), 1 650 (C=O), and 1 603  $cm^{-1}$  (C=N) (Found: C, 55.3; H, 3.5; N, 14.2.  $C_9H_7ClN_2O$  requires C, 55.5; H, 3.6; N, 14.4%);  $\delta(CDCl_3)$  4.0 (1 H, d, 5-H), 5.0br (1 H, exchanges with  $D_2O$ , NH), 5.6 (1 H, q, 6-H), 7.0 (1 H, q, 7-H), 7.4 (1 H, d, 4-H), 8.3 (1 H, d, 3-H), and 8.8 (1 H, s).

*Photolysis of 7-chloro-4-quinolyl azide.* The azide (1 g) in methanol (60 ml)-tetrahydrofuran (60 ml) was irradiated for 8 h in a Pyrex apparatus. The solvent was evaporated and the residue chromatographed on alumina. Elution with chloroform gave 4-azo-7-chloroquinoline (0.8 g, 94%), m.p. 214 °C (Found: C, 61.5; H, 2.9; N, 16.2.  $C_{18}H_{10}Cl_2N_4$  requires C, 61.2; H, 2.9; N, 15.9%);  $\nu_{max}$  (Nujol) 1 605  $cm^{-1}$  (C=N);  $\delta(CDCl_3)$  7.7 (2 H, d, 3-H), 7.9 (2 H, dd, 6-H), 8.3 (2 H, d, 5-H), 8.4 (2 H, d, 8-H), and 8.9 (2 H, d, 2-H).

*Reactions of 7-Methoxy-5H-pyrido[3,2-c]azepine with Amines.*—(a) *With diethylamine.* A solution of the azepine (5) in diethylamine (10 ml), ethanol (10 ml), and acetic acid (2 ml) was heated at reflux (79 °C) for 12 h. The solution was evaporated to dryness and chromatographed over alumina. Elution with toluene gave 7-diethylamino-5H-pyrido[3,2-c]azepine (5;  $Et_2N$  for MeO) (0.3 g, 79%), m.p. 74 °C, white crystals [light petroleum (b.p. 40–60 °C)] (Found: C, 72.5; H, 7.95; N, 19.7.  $C_{13}H_{17}N_3$  requires C, 72.5; H, 7.95; N, 19.5%);  $\nu_{max}$  (Nujol) 1 620  $cm^{-1}$  (C=N);  $\delta(CDCl_3)$  8.55 (1 H, dd, 2-H), 7.31 (1 H, dd, 3-H), 7.65 (1 H, dd, 4-H), 7.35 (1 H, d, 9-H), 6.75 (1 H, d, 8-H), 4.15 (2 H, s,  $CH_2$ ), 3.3 [4 H, q,  $(CH_2)_2$ ], and 1.1 [6 H, t,  $(CH_3)_2$ ];  $m/e$  215 ( $M^+$ ).

(b) *With cyclohexylamine.* A solution of the azepine (5) (0.4 g) in cyclohexylamine (20 ml) was heated at reflux for 9 h at 134 °C. The solution was evaporated to dryness and chromatographed over alumina. Elution with light petroleum-toluene (1 : 1) gave starting material (0.02 g, 5%). Further elution with toluene-ethyl acetate gave 7-cyclohexylamino-5H-pyrido[3,2-c]azepine (5;  $C_6H_{11}N$  for MeO) (0.45 g, 85%), m.p. 187 °C, white crystals (light petroleum : ethyl acetate 1 : 1) (Found: C, 74.5; H, 7.8; N, 17.2.  $C_{15}H_{19}N_3$

requires C, 74.65; H, 7.9; N, 17.4%);  $\nu_{max}$  (Nujol) 3 250 (NH) and 1 600  $cm^{-1}$  (C=N);  $\delta(CDCl_3)$  8.54 (1 H, dd, 2-H), 7.22 (1 H, dd, 3-H), 7.66 (1 H, dd, 4-H), 7.28 (1 H, d, 9-H), 6.44 (1 H, d, 8-H), 4.2 (2 H, s,  $CH_2$ ), 4.0 (1 H, exchanges with  $D_2O$ , NH), 3.6 (1 H, bs, CH), and 2.0–1.0 [10 H, bm,  $(CH_2)_5$ ];  $m/e$  241 ( $M^+$ ).

(c) *With aniline.* A solution of the azepine (5) (0.4 g) in aniline (10 ml) was heated at 150 °C for 3 h. The solution was evaporated to dryness and chromatographed over alumina. Elution with toluene gave 7-anilino-5H-pyrido[3,2-c]azepine (5;  $C_6H_5NH$  for MeO) (0.4 g, 73%), m.p. 183 °C cream prisms (light petroleum-ethyl acetate 1 : 1) (Found: C, 76.6; H, 5.6; N, 17.95.  $C_{15}H_{13}N_3$  requires C, 76.6; H, 5.6; N, 17.9%);  $\nu_{max}$  (Nujol) 3 300 (NH) and 1 590  $cm^{-1}$  (C=N);  $\delta(CDCl_3)$  8.6 (1 H, dd, 2-H), 7.25 (1 H, dd, 3-H), 7.55 (1 H, dd, 4-H), 7.25 (1 H, d, 9-H), 6.60 (1 H, d, 8-H), 5.2 (1 H, exchanges with  $D_2O$ , NH), 4.15 (2 H, s,  $CH_2$ ), and 7.3–7.0 (5 H, bm, phenyl);  $m/e$  235 ( $M^+$ ).

(d) *With water-dioxan.* A solution of the azepine (5) (0.4 g) in water (5 ml) and dioxan (5 ml) was heated at 100 °C for 3 h. The solution was evaporated to dryness and the residue crystallised from light petroleum-ethyl acetate (1 : 1) to give the azepinone (6) (0.33 g, 90%), m.p. 164 °C, white plates, identical with an authentic sample.

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## REFERENCES

- 1 B. Iddon, O. Meth-Cohn, E. F. V. Scriven, H. Suschitzky, and P. T. Gallagher, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 900.
- 2 H. Suschitzky, *Heterocyclic Lectures*, 1980, **5**, 1.
- 3 F. Hollywood, E. F. V. Scriven, H. Suschitzky, D. R. Thomas, and R. Hull, *J. Chem. Soc., Chem. Commun.*, 1978, 806.
- 4 J. Rigaudy, C. Igier, and J. Barcelo, *Tetrahedron Lett.*, 1975, 3845.
- 5 J. Rigaudy, C. Igier, and J. Barcelo, *Tetrahedron Lett.*, 1979, 1837.
- 6 R. J. Sundberg and R. H. Smith, *J. Org. Chem.*, 1971, **36**, 295; A. C. Mair and M. F. G. Stevens, *J. Chem. Soc. C*, 1971, 2317; R. Purvis, R. K. Smalley, W. A. Strachan, and H. Suschitzky, *J. Chem. Soc., Perkin Trans., 1*, 1978, 191; S. Senda, K. Hirota, and T. Asao, *Tetrahedron Lett.*, 1978, 1531.