The Synthesis of some Pyrido[1,4]benzoxazepines and a Dipyrido[1,4]oxazepine

Keith Brewster, John M. Harrison and Thomas D. Inch

Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, SP4 0JQ, U.K.

Received February 2, 1978

Synthetic routes to pyrido[2,3-*b*]-, pyrido[4,3-*b*]-, pyrido[3,2-*f*][1,4]benzoxazepines and dipyrido[2,3-*b*:2,3-*f*][1,4]oxazepine are described. The applicability of one of the methods to dibenz[*b*,*f*][1,4]oxazepine synthesis is discussed.

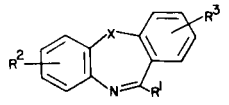
J. Heterocyclic Chem., 15, 1497 (1978)

The synthesis of many variously substituted dibenz[*b*,*f*][1,4]oxazepines, thiazepines and diazepines with general structure **1** have been reported (1). These compounds possess a wide range of pharmacological properties. More specifically, compounds of this general structure are potent sensory irritants (1) when R^1 = H but not when R^1 is any other substituent. Some aspects of the chemistry and biological evaluation of the parent compound **1** (X = O, R^1 = R^2 = R^3 = H) have been described (1,2). We now report the synthesis of some new analogues in which one or both benzene rings are replaced by the pyridine ring system, *viz.* **6**, **10**, **16** and **20**.

Two methods of synthesis were used. The first procedure (see Schemes 1 and 2) utilised conventional methods with Ullmann condensation of a chloronitropyridine with salicylaldehyde to afford a nitroaldehyde which on reduction with ferrous sulphate and ammonia gave an aminoaldehyde which spontaneously ring closed to the pyridobenzoxazepine. Thus, pyrido[2,3-*b*][1,4]benzoxazepine (**6**) was prepared (Scheme 1) from 2-chloro-3-nitropyridine (**2**) and salicyladehyde (**3**) *via* nitroaldehyde **4** and aminoaldehyde **5**. Similarly, pyrido[4,3-*b*][1,4]benzoxazepine (**10**) was prepared (Scheme 2) from 4-chloro-3-nitropyridine (**7**) and **3**.

The second method required the synthesis of the appropriate Schiffs' base **12**, **16** or **19** which were ring-closed by treatment with sodium hydride in dimethylformamide (see Schemes 3-5). Thus **6** was also prepared (Scheme 3) from **12** obtained by the condensation of **3** with 2-chloro-3-aminopyridine (**11**). Pyrido[3,2-*f*][1,4]-benzoxazepine (**16**) and dipyrido[2,3-*b*:2,3-*f*][1,4]oxazepine (**20**) were obtained by corresponding procedures (Schemes 4 and 5, respectively).

The ring closure of Schiffs' bases under mild conditions demonstrates the high reactivity of 2-chloropyridines towards nucleophiles relative to that of corresponding benzene analogues, and provides a convenient synthesis of pyridooxazepines (3) that is applicable to dibenzoxazepine synthesis in the presence of suitably placed activating substituents. Attempts to prepare **1** (X = O, R^1 = R^2 = R^3 = H) from **21** were completely unsuccessful. Similarly, **22** failed to yield any dibenzoxazepine. However, **23** on treatment with base returned a high yield of 8-nitro[*b*,*f*]-



X = O, S, NR^4

1

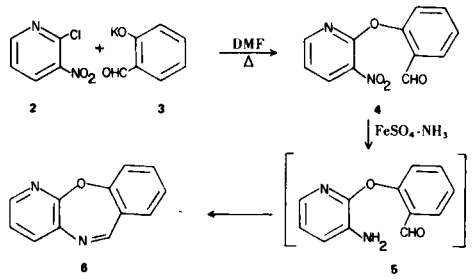
[1,4]oxazepine. Similarly, **24** gives the 2-nitro analogue (4,5). Both reactions reflect the enhanced reactivity of chlorine to nucleophilic aromatic substitution as a consequence of the *p*-nitro group (6).

EXPERIMENTAL

Spectroscopic data (^{1}H nmr, ir and ms) are not reported but for all compounds were fully consistent with proposed structures.

Pyridooxazepines **6**, **10** and **16** are sensory irritants and should be handled accordingly. The dipyridooxazepine (**20**) is non-irritant.

Scheme 1



2 **3** **4** **5** **6**

2-(2^1-Formylphenoxy)-3-nitropyridine (**4**).

Compound **3** (5.0 g., 0 031 mole) and **2** (5.0 g., 0.032 mole) were heated under reflux in DMF (100 ml.) for 3 hours. The mixture was cooled, poured into water and the resulting crystals filtered off and dried. Recrytallisation from ethanol gave 2-(2^1-formylphenoxy)-3-nitropyridine (**4**), 4.5 g., (60%) m.p. 104°.

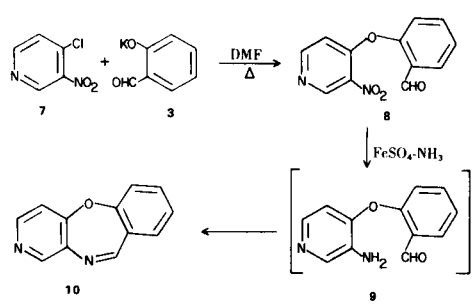
Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.09; H, 3.43; N, 11.58.

Pyrido[2,3-*b*][1,4]benzoxazepine (**2**).

Compound **4** (1.5 g., 0.0061 mole) was added to a solution of ferrous sulphate (15 g.) in water (40 ml.). The mixture was boiled for 10 minutes, cooled to 70° and ethanol (40 ml.) and 0.880 ammonia (15 ml.) added and then boiled for 1 hour. The solid was filtered off and both solid and filtrate extracted with chloroform. The extracts were combined, dried and concentrated and the residue chromatographed over silica with ether-petrol-ethanol (4:5:1) to give after recrystallisation from light petroleum, pyrido[2,3-*b*][1,4]benzoxazepine (**2**), 0.74 g., (62%) m.p. 75-76°.

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.21; H, 4.21; N, 14.55.

Scheme 2



4-(2^1-Formylphenoxy)-3-nitropyridine (**8**).

As described above, Ullmann condensation of **7** (5.0 g., 0.032 mole) with **3** (5.0 g., 0.032 mole) gave 4-(2^1-formylphenoxy)-3-nitropyridine (**8**), 4.1 g., (54%) m.p. 100-101° from benzene-petrol.

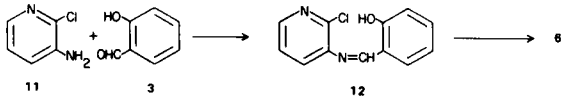
Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.28; H, 3.45; N, 11.55.

Pyrido[4,3-*b*][1,4]benzoxazepine (**10**).

Reduction of **8** (3.5 g., 0.014 mole) with ferrous sulphate and ammonia as above gave pyrido[4,3-*b*][1,4]benzoxazepine (**10**), 0.78 g., (28%) m.p. 102° from cyclohexane.

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.31; H, 4.06; N, 14.03.

Scheme 3



N-(2^1-Hydroxybenzylidene)-3-amino-2-chloropyridine (**12**).

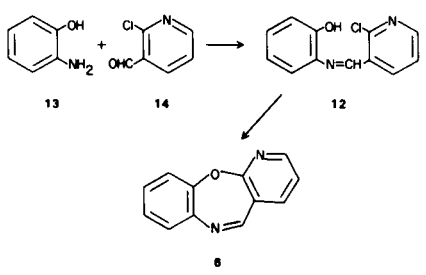
Compound **11** (1.5 g., 0.012 mole) and (1.5 g., 0.012 mole) in ethanol (20 ml.) were boiled under reflux for 2 hours. The solvent was evaporated and the residue recrystallized from ethanol to give *N*-(2^1-hydroxybenzylidene)-3-amino-2-chloropyridine (**12**) 2.0 g., (72%) m.p. 70°.

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.54; H, 3.84; N, 12.29.

Pyrido[2,3-*b*][1,4]benzoxazepine (**2**).

Compound **12** (1.0 g., 0.0043 mole) and sodium hydride (0.5 g.) in dry DMF was stirred at 70° for 40 minutes. Work up and purification as above gave **2**, 0.56 g. (66%).

Scheme 4



N-(2^1-Chloropyrid-3-ylmethylidene)-2-hydroxyaniline (**15**).

2-Chloronicotinic acid was converted into 2-chloro-3-hydroxymethylpyridine by the method of Zeigler and Sweeny (7) and oxidised with manganese dioxide according to Heinart and Martell (8) to give 2-chloro-3-formylpyridine (**14**). Condensation of **14** (0.5 g., 0.0035 mole) with **13** (0.38 g., 0.0035 mole) in the usual way gave *N*-(2^1-chloropyrid-3-ylmethylidene)-2-hydroxyaniline (**15**), 0.67 g., (83%) m.p. 158-160° from ethanol.

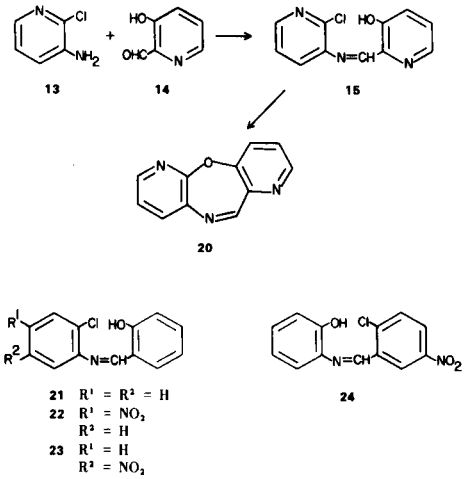
Anal. Calcd. for $C_{12}H_9ClN_2O$; C, 61.95; H, 3.90; N, 12.04. Found: C, 61.70; H, 3.94; N, 12.00.

Pyrido[3,2-*f*][1,4]benzoxazepine (**16**).

Compound **15** (1.5 g., 0.0065 mole) was treated with sodium hydride (0.16 g.) in dry DMF (15 ml.) at 50° for 3 hours to give in the usual way, pyrido[3,2-*f*][1,4]benzoxazepine (**16**), 0.68 g. (53%) m.p. 129-131° from ethanol.

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.07; H, 4.28; N, 13.91.

Scheme 5



21 $R^1 = R^2 = H$
22 $R^1 = NO_2$, $R^2 = H$
23 $R^1 = H$, $R^2 = NO_2$

N-(3^1-Hydroxypyrid-2^1-ylmethylidene)-3-amino-2-chloropyridine (**19**).

The Schiffs' base from **17** (1.29 g., 0.01 mole) and **18** (1.23 g., 0.01 mole) was prepared in the usual way to give **19**, 1.9 g., (82%) m.p. 146° from ethanol.

Anal. Calcd. for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98. Found: C, 56.20; H, 3.51; N, 17.96.

Dipyrido[2,3-*b*:2,3-*f*][1,4]oxazepine (**20**).

Compound **19** (1.0 g., 0.0043 mole) and sodium hydride (0.2 g.) in dry DMF (10 ml.) were stirred at 60° for 3 hours. Addition to water and continuous extraction with chloroform gave after chromatography over silica with chloroform-ethanol (9:1), dipyrido[2,3-*b*:2,3-*f*][1,4]oxazepine (**20**), 0.22 g. (26%) m.p. 225° from ethanol. Whilst satisfactory analytical data could not be obtained from **20**, spectroscopic data were fully consistent with the proposed structure and together with chromatographic studies, indicated that the product was homogeneous.

8-Nitrodibenz[*b*,*f*][1,4]oxazepine.

Condensation of 2-chloro-5-nitroaniline (1.7 g., 0.01 mole) with **3** (1.2 g., 0.01 mole) in the usual way gave *N*-(2^1-hydroxybenzylidene)-2-chloro-5-nitroaniline (**23**), 2.2 g., (80%) m.p. 176° from ethanol.

Anal. Calcd. for $C_{13}H_9ClN_2O_3$: C, 56.43; H, 3.28; N, 10.13. Found: C, 56.10; H, 3.35; N, 10.00.

Treatment of **23** (1.0 g., 0.0036 mole) with sodium hydride in DMF for 2 hours at 50° gave 8-nitrodibenz[*b*,*f*][1,4]oxazepine,

0.67 g., (79%) m.p. 177° from ethanol.

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.0; H, 3.4; N, 11.7. Found: C, 64.9; H, 3.81; N, 11.72.

NOTES AND REFERENCES

(1) A. W. H. Wardrop, G. L. Sainsbury, J. M. Harrison and T. D. Inch, *J. Chem. Soc., Perkin Trans. I*, 1279 (1976) and references therein.

(2) K. Brewster, R. A. Chittenden, J. M. Harrison and T. D. Inch, *ibid.*, 1291 (1976).

(3) Similar procedures have been reported for the preparation of pyridobenzoxazepinones, thiazepinones and diazepinones. See for example: C. Hoffmann and A. Faure, *Bull. Soc. Chim. France*, 2316 (1966); K. Thomae, British Patent 1,050-565, Dec. 7, 1966; *Chem. Abstr.*, **66**, 37915r (1967); G. Schmidt, U. S. Patent 3,406,168, Oct. 15, 1968; *Chem. Abstr.*, **70**, 87866d (1969).

(4) CIBA Ltd., Netherlands Appl. 6,606, 671, Dec. 27, 1966; *Chem. Abstr.*, **67**, 90856u (1967).

(5) K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni and R. K. Shah, *Indian J. Chem.*, **12**, 227 (1974).

(6) Presumably, an *o*-nitro group would provide comparable activation.

(7) F. Zeigler and J. Sweeny, *J. Org. Chem.*, **34**, 11 (1969).

(8) D. Heinart and A. Martell, *Tetrahedron*, 49 (1958).