Tetrahedron Vol 39, No 3, pp 479 to 481, 1983
Printed in Great Britain

0400-4020/83/030479-03$03 00/0

BENZOXADIAZOCINES, BENZOTHIADIAZOCINES AND BENZOTRIAZOCINES—I

GENERAL CONSIDERATIONS AND THE SYNTHESIS OF TWO 3,1,6-BENZOXADIAZOCINES

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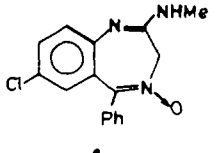
(*Received in U.K.* 19 *April* 1982)

Abstract—A general method of synthesis for derivatives of the novel 3,1,6-benzoxadiazocine, 3,1,6-benzothiadiazocine and 1,3,6-benzotriazocine ring systems is described, and the method is applied for the preparation of two 3,1,6-benzoxadiazocine derivatives.

The discovery of the potent tranquilizers Chlorodiazepoxide (Librium®, **1**) and Diazepam (Valium®, **2**) has stimulated the synthesis and pharmacological screening of a great number of related substances—among them compounds having the two N atoms in other than positions 1 and 4 of the 7-membered ring,† or containing additional heteroatoms or heterorings of different size—in many laboratories all over the world.



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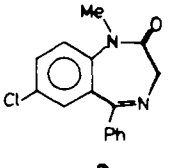

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Strikingly, a comparatively small number of benzo-condensed derivatives of 8-membered heterocycles containing three heteroatoms, among them at least two N atoms, is known. 1,3,6-[4,5] and 4,1,5-Benzoxadiazocine derivatives[6,7] have been studied mainly by Sternbach's group, and 2,1,5-benzothiadiazocine derivatives by Austrian scientists.[8–10] Some derivatives of the 1,2,5-[11,12] and 1,4,5-benzothiadiazocine ring systems[13] are also known. The 1,4,5-benzotriazocine system has been studied rather extensively, mainly in Japanese laboratories.[14–23]

We have therefore decided to synthesize a series of derivatives of the hitherto unknown 3,1,6-benzoxadiazocine (**4a**, **5a**), 3,1,6-benzothiadiazocine (**4b**, **5b**) and 1,3,6-benzotriazocine ring system (**4c**, **5c**) for pharmacological screening. The strategy conceived for the preparation of these compounds consisted in the synthesis of the precursors **3a–c** which, with the exception of either the C atom in position 2 or the C and X atoms in positions 2 and 3, already contained all ring atoms of the desired compounds, and subsequent ring closure with the aid of suitable C_1 and C–X components, respectively (Chart 1).

In order to avoid ring closure in the wrong direction (**3**→**6**) as well as, after ring closure in the desired direction (**3**→**4** or **5**), subsequent ring contraction (e.g. **4**→**7**; Chart 1), the nucleophilicity of the R-substituted N atom in **3** and **4**, respectively, had to be kept as low as possible. Therefore we started our studies with type **3** compounds in which R is an alkyl- or arylsulfonyl group.

In the present paper we report on the application of the above method for the synthesis of two 3,1,6-benzoxadiazocine derivatives; in the accompanying papers the syntheses of type **4** and **5** compounds with X = NH or NR' and S, R = $MeSO_2$–, $ArSO_2$– will be described.

The method of synthesis of the benzoxadiazocine derivatives **12** and **13** is shown in Chart 2. For details see Experimental.

EXPERIMENTAL

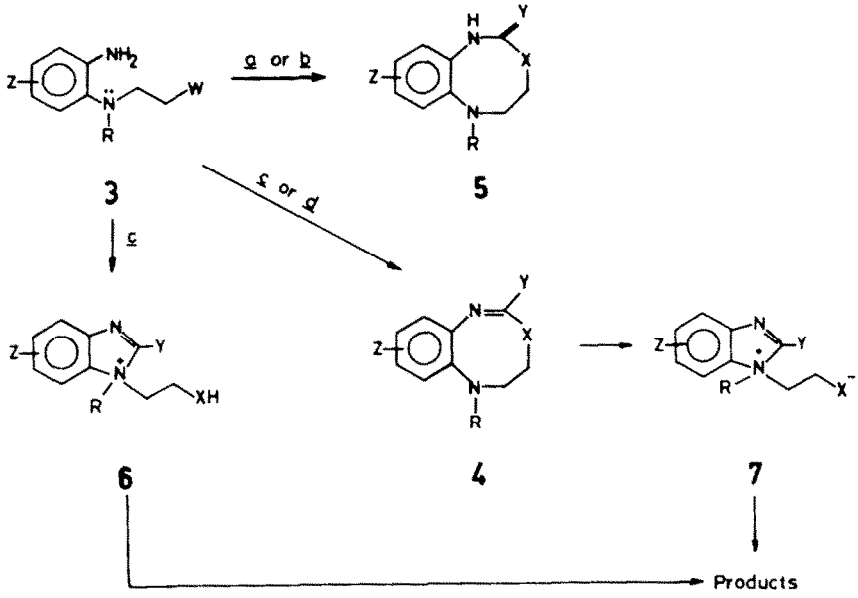
IR spectra were obtained in KBr pellets using Perkin–Elmer Model 421 and Spectromom Model 2000 (Hungarian Optical Works, Budapest) spectrometers. ^{1}H NMR spectra were obtained at 60 MHz using a Perkin–Elmer Model R-12 spectrometer.

N - (2 - *Hydroxyethyl*) - 4' - *methoxy* - 2' - *nitrotosylanilide* (**9**). Compound **8**[24] (33.6 g; 0.1 mmol) was added to a soln of Na (2.3 g; 0.1 mol) in dry MeOH (200 ml). The mixture was refluxed for 0.5 hr and concentrated to 1/3 its volume to obtain the Na salt of **8** (30 g; 84%) in the form of red crystals which were filtered off and washed with ether.

The Na salt was dissolved in DMF (100 ml). 2-Chloroethanol (12 g; 0.15 mol) was added, and the mixture was stirred for 10 hr at 120° and poured into 400 ml soln of NaOH (2 g) to obtain the light yellow crystals (22.5 g; 61.5%) of the title compound, m.p. 121–122° from CH_2Cl_2–pentane. (Found: C, 52.54; H, 5.20; N, 7.47. $C_{16}H_{18}N_2O_6S$ (366.4) requires: C, 52.45; H, 4.95; N, 7.65%.)

2' - *Amino* - N - (2 - *hydroxyethyl*) - 4' - *methoxytosylanilide* (**10**). A soln of **9** (18.8 g; 50 mmol) in 2-propanol (250 ml) was reduced at normal pressure and room temp. in the presence of a 8% Pd-C catalyst (2 g). The catalyst was filtered off and the oily residue was triturated with ether to obtain the colourless crystals (15.5 g; 92%) of the title compound, m.p. 85–87° from EtOH.

†For reviews on diazepines and benzodiazepines, see Refs. 1–3.



a: X = O
b: X = S
c: X = NH or NR′ W = Hlg, -XH

a: C=Y component (when W = XH)
b: C(=Y)(-X) component (when W = leaving group)
c: C-Y component (when W = XH)
d: C(-Y)(-X) component (when W = leaving group)

Chart 1.

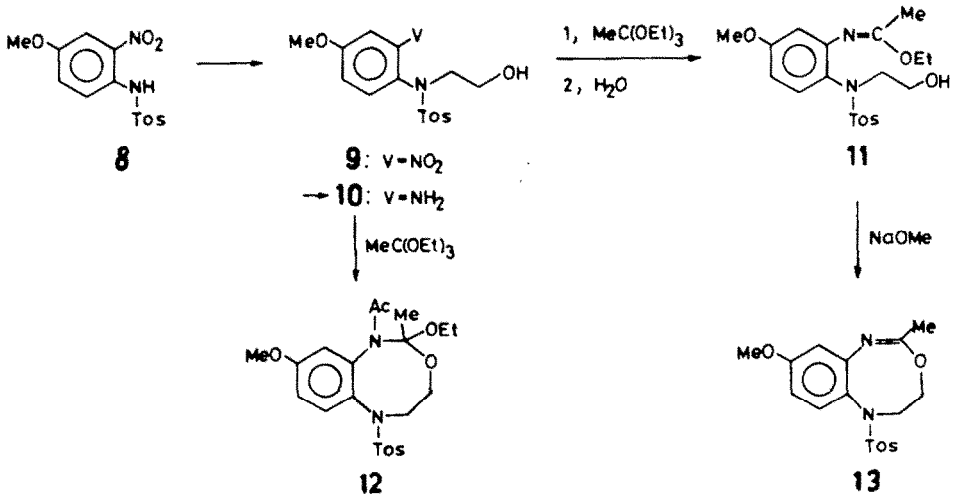


Chart 2.

(Found: N, 8:14; S, 9.78%. $C_{16}H_{20}N_2O_4S$ (336.4) requires: N, 8.33; S, 9.53%.)

The *hydrochloride* was obtained by dissolving the amine (3.4 g; 10 mmol) in EtOH (30 ml), previously saturated with dry HCl at 0°, and precipitating the colourless crystals, m.p. 202–203° (dec), of the salt (3.4 g; 91%) by adding hexane to the soln. (Found: Cl, 9.69; N, 7.62; S, 8.87%. $C_{16}H_{21}ClN_2O_4S$ (373.9) requires: Cl, 9.51; N, 7.51; S, 8.60%.)

Ethyl N - {2 - [N - (2 - *hydroxyethyl*) - N - *tosylamino*] - 4 - *methoxyphenyl*}*acetamidate* (**11**). A mixture of **10** (3.4 g; 10 mmol) and triethyl orthoacetate (10 ml) was refluxed for 6 hr and evaporated to dryness *in vacuo*. The residue was stirred at

room temp. for 2 days with ether (50 ml) saturated previously with water. The mixture was evaporated to dryness and the crystalline residue was triturated with a small amount of ether to obtain 2.0 g (49%) of the title compound, m.p. 116–117° from CH_2Cl_2–pentane. (Found: C, 58.84; H, 6.42; N, 7.09; S, 8.04%; $M^{+\cdot}$ 406.15289. $C_{20}H_{26}N_2O_5S$ (406.5) requires: C, 59.09; H, 6.44; N, 6.89; S, 7.89%; M, 406.15623.)

IR: 3350, 1670, 1350, 1290, 1160 cm^{-1}; ^1H NMR (CCl_4): δ 1.42t + 4.22q (J = 7.1 Hz); 2.00s; 2.46s; 3.74s; 6.27–6.45m; 7.27 + 7.60 (AA'BB'; J = 8.5 Hz).

Alcoholysis. An anhyd. ethanolic (10 ml) soln of **11** (0.4 g) was saturated with dry HCl at 0°. Upon addition of ether 0.4 g of **10**·HCl, m.p. 202–203° (from EtOH–ether), identical with the authentic sample obtained as described above, was precipitated.

1 - *Acetyl* - 2 - *ethoxy* - 9 - *methoxy* - 2 - *methyl* - 6 - *tosyl* - 1,4,5,6 - *tetrahydro* - 2H - 3,1,6 - *benzoxadiazocine* (**12**). The mixture of **10** (3.4 g; 10 mmol) and triethyl orthoacetate (10 ml) was refluxed for 6 hr and evaporated to dryness *in vacuo*. The residue was triturated with three portions (30 ml, each) of pentane to obtain the colourless crystals (3.5 g; 78%) of the title compound, m.p. 85–87° from hexane. (Found: C, 59.01; H, 6.79; N, 6.35; S, 6.75. $C_{22}H_{28}N_2O_6S$ (448.3) requires: C, 58.90; H, 6.24; N, 6.25; S, 7.15%.)

IR: 1660, 1345, 1275, 1155 cm^{-1}; ^1H NMR (CCl_4): δ 1.07t + 1.32t (total intensity 3H) + 4.17q (J = 7.5 Hz); 1.25s; 1.85s; 2.44s; 3.25–3.70m; 3.78s; 6.25–7.10m; 7.42 + 7.86 (AA'BB'; J = 8.5 Hz).

Hydrolysis. A mixture of **12** (0.45 g) and 20% HClaq. (10 ml) was stirred for 2 days at room temp. and evaporated to dryness *in vacuo*. The residue was dried and recrystallized from EtOH–hexane to obtain 0.3 g of **10**·HCl, m.p. 202–203°, identical with the authentic sample obtained as described above.

9 - *Methoxy* - 2 - *methyl* - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzoxadiazocine* (**13**). A mixture of **11** (0.4 g; 1 mmol), anhyd. dioxane (20 ml) and a trace of NaOMe was refluxed for 8 hr, filtered after cooling and evaporated to dryness. The residue was worked up by prep. TLC (Kieselgel $PF_{254-366}$, cyclohexane–EtOAc, 7:3; eluent: CH_2Cl_2) to obtain 0.2 g (55%) of the title compound, m.p. 169–170° from CCl_4. (Found: C, 59.70; H, 5.54; N, 8.04; S, 8.43. $C_{18}H_{20}N_2O_4S$ (360.5) requires: C, 59.97; H, 5.59; N, 7.77; S, 8.89%.)

IR: 1700, 1345, 1230, 1160 cm^{-1}; ^1H NMR (CCl_4): δ 1.68s; 2.47s; 3.78s; 6.35–7.00m; 7.18 + 7.55 (AA'BB'; J = 8 Hz).

Acknowledgement—Financial support of EGyT Pharmacochemical Works, Budapest, is gratefully acknowledged.

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