

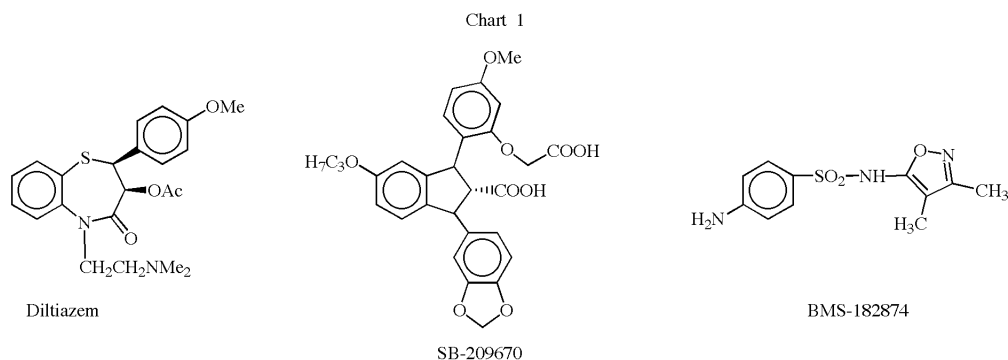
[a] Laboratoire de Chimie Thérapeutique; [b] Service Commun de RMN;  
 Département de Pharmacochimie Moléculaire, UMR 5063-CNRS,  
 Faculté de Pharmacie - Université J. Fourier - 38706 La Tronche Cedex - France  
 Received July 27, 2000

A series of 3-carboxylic derivatives of disubstituted 1,5-benzodiazepines (**5-9**) was synthesized by heterocyclisation from 1,2-diaminobenzene (**1**) with dibenzoylmethane (**2**) followed by bromination on position 3 and by introduction of the carboxylic group or introduction of the malonic moiety. Reduction of the heterocycle gave the perhydro derivative diethyl (2,4-diphenyl-1,2,4,5-tetrahydro-3*H*-1,5-benzodiazepin-3-yl)malonate (**9**).

*J. Heterocyclic Chem.*, **38**, 641 (2001).

Calcium channel blockers as diltiazem [1-2] and endothelin antagonists namely SB-209670 [3] and BMS-182874 are protective cardiovascular agents acting by coronary vasodilatation and activation of coronary blood flow [4-6] (Chart 1). Comparison of their structures prompted us to design novel protective agents with a mixed structure.

It was not possible to obtain the heterocyclization from 1,2-diaminobenzene and a diaryl  $\beta$ -diketone when this  $\beta$ -diketone bears also an ester or a cyano or a carboxylic moiety on the  $\alpha$ -atom. Therefore the carboxylic moiety had to be introduced by carboxylation of the 3-bromo derivative *via* an organometallic reaction. However the introduction of the ester (ethoxycarbonyl) group or the



We wish to describe herein the synthesis of 3-carboxylic derivatives of diaryl substituted 1,5-benzodiazepines which at present are being tested for their coronary vasodilator properties.

Among thousands of benzodiazepinic compounds, those bearing a carboxylic group or derived moiety are very few. The best known are chlorazepic acid and ethyl loflazepate which are anxiolytics having a 1,4-benzodiazepine structure. 1,5-Benzodiazepine derivatives are much fewer, and none bearing a carboxylic or an ester group at the 3-position is described.

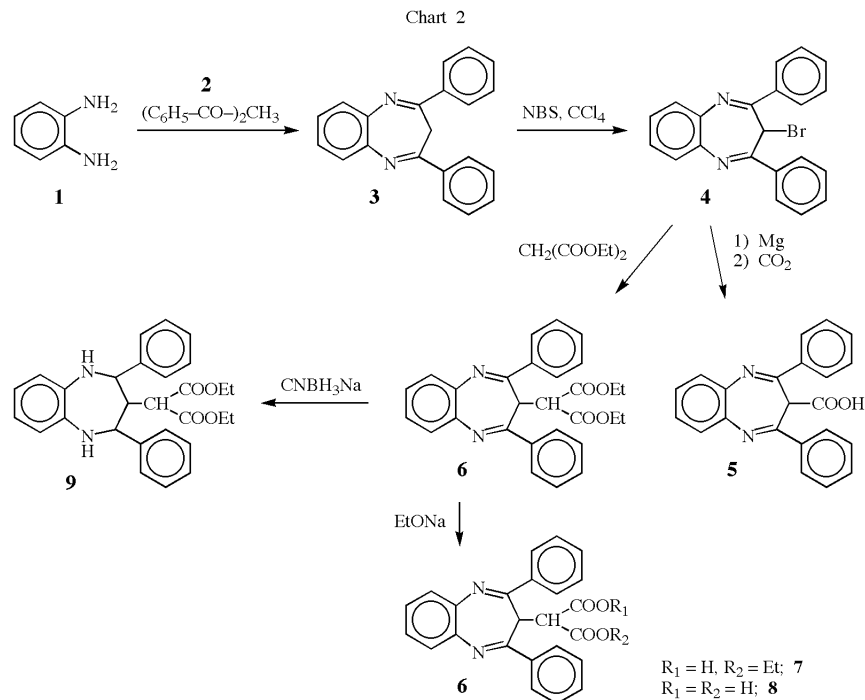
The 1,5-benzodiazepine heterocycle was constructed in a one pot operation from 1,2-diaminobenzene (**1**) by cyclization with dibenzoylmethane (**2**) (Chart 2). The carboxylic or the ester group in the 3-position of 1,5-benzodiazepine compounds could be introduced during the construction of the heterocyclic moiety as in the 1,4-benzodiazepine series or by substitution of a 3-bromo-1,5-benzodiazepine derivative to give the corresponding monocarboxylic acid or the malonic acid or the malonic ester derivative.

cyano moiety in this 3-position was always unsuccessful even from 3-unsubstituted-1,5-benzodiazepine structure or from 3-bromo-1,5-benzodiazepine structure.

The preparation of 3-carboxylic derivatives of 2,4-diphenyl-3*H*-1,5-benzodiazepine was achieved by cyclization of 1,2-diaminobenzene (**1**) with dibenzoylmethane (**2**) which afforded 2,4-diphenyl-3*H*-1,5-benzodiazepine (**3**). Its bromination by *N*-bromosuccinimide gave

3-bromo-2,4-diphenyl-1,5-3*H*-benzodiazepine (**4**). The introduction of the carboxylic moiety in the 3 position was obtained from (**4**) by the Grignard reaction using solid carbon dioxide to give 2,4-diphenyl-3*H*-1,5-benzodiazepin-3-carboxylic acid (**5**). Malonic derivatives were obtained by condensation of (**4**) with diethyl malonate to give the diethyl ester of (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonic acid (**6**). Partial saponification of this diester gave the monoacid derivative (**7**). The diacid (**8**) was obtained by longer hydrolysis.

The heterocyclic moiety of the diester (**6**) could be reduced by sodium cyanoborohydride by a procedure



adapted from Ohkawa *et al.* [8] giving diethyl (2,4-diphenyl-1,5-benzoperhydroazepin-3-yl) malonate (**9**).

In theory, the reduction of (**6**) that contains 2 double bonds, in the case of an attack by  $\text{H}^-$  ion from sodium cyanoborohydride on the same side of the double bond, could lead to (**9**) that should be a mixture of the *cis* isomers which are enantiomers. In the case of an attack of  $\text{H}^-$  to each side of the heterocycle, a mixture of 4 diastereoisomers (2 enantiomer pairs) could be obtained because of the prochirality of the carbon-3 in the compound (**6**), which becomes a chiral carbon in the compound (**9**).

Experimentally we have isolated only one product with good yield (85%) which has led us to believe that the reduction follows the first hypothesis.

## EXPERIMENTAL

Melting points were determined with a Buchi 510 capillary apparatus and are uncorrected. The ir spectra were recorded on a Unicam SP 1100 infrared spectrophotometer using potassium bromide plates for solid products. The frequencies are expressed in  $\text{cm}^{-1}$ .  $^1\text{H}$  and  $^{13}\text{C}$ -nmr spectra were obtained on a Bruker AC 200 spectrometer in deuteriochloroform or dimethylsulfoxide- $d_6$  solution. Chemical shifts are given in  $\delta$  (ppm) units relative to the internal reference tetramethylsilane. The abbreviations of signal patterns are as follows: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad. Elemental analyses (C, H, N, Br, O) were carried out in the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69 390 Vernaison, France and were within  $\pm 0.4\%$  of theoretical values unless otherwise noted. Reaction progress and purity of products were checked by carrying out tlc using silica gel Merck 60 F254; the spots were visualised by uv and iodine vapour.

2,4-Diphenyl-3H-1,5-benzodiazepine (**3**).

A mixture of 1,2-diaminobenzene (**1**) (12.9 g, 120 mmoles) and dibenzoylmethane (**2**) (22.4 g, 100 mmoles) was heated at 170-180° for 4 hours. After evaporation of the mixture and mixing with diethyl ether a precipitate was obtained. The crude product was collected, dried, and recrystallized from ethanol to give 9.86 g (44%) of 2,4-diphenyl-3H-1,5-benzodiazepine (**3**), mp 138° (lit. 140° [9]);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  3.74 (br s, 2H, 3-H<sub>2</sub>), 7.36 (dd, 2H, 6-,9-H,  $J = 6.1, 3.5$  Hz), 7.41- 7.43 (m, 6H, *m, p*- phenyl protons), 7.63 (dd, 2H, 7-,8-H,  $J = 6.1, 3.5$  Hz), 7.96-8.01 (m, 4H, *o*-phenyl protons); ir (potassium bromide): 1580 (C=N)  $\text{cm}^{-1}$ .

3-Bromo-2,4-diphenyl-3H-1,5-benzodiazepine (**4**).

A mixture of 2,4-diphenyl-3H-1,5-benzodiazepine (**3**) (0.6 g, 2 mmoles) in tetrachloro-carbone (2.4 ml) and *N*-bromosuccinimide (0.48 g, 2.6 mmoles) was refluxed without benzoyl peroxid under nitrogen atmosphere for 16 hours. After cooling to room temperature, the crude product was filtered, dried, and recrystallized from dry ether to give 0.54 g (90%) of 3-bromo-2,4-diphenyl-3H-1,5-benzodiazepine (**4**), mp 120°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  7.02 (s, 1H, 3-H), 7.46-7.51 (m, 8H, 6-, 9-H, *m, p*-phenyl protons), 7.71 (dd, 2H, 7-, 8-H,  $J = 6.1, 3.5$  Hz), 7.90-7.95 (m, 4H, *o*-phenyl protons); ir (potassium bromide): 1580 (C=N), 730 (C-Br)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{15}\text{BrN}_2$ : C, 67.45; H, 4.04; Br, 21.36; N, 7.49. Found: C, 67.37; H, 4.00; Br, 21.02; N, 7.46.

2,4-Diphenyl-3H-1,5-benzodiazepin-3-carboxylic acid (**5**).

Carboxylation of (**4**) was performed with experimental conditions adapted from the literature [7]. A mixture of magnesium (0.08 g, 3.3 mmoles), 3-bromo-2,4-diphenyl-3H-1,5-benzodiazepine (**4**) (1g, 2.66 mmoles) and tetrahydrofuran (6 ml) was refluxed under a nitrogen atmosphere for 4 hours. After cooling to room temperature,

solid carbon dioxide was introduced for 45 minutes, then water (2 ml) was added. The reaction mixture was acidified by 10% (v/v) hydrochloric acid, extracted by ethyl acetate. The aqueous solution was evaporated. The residue was washed with methanol. After evaporation of the solvent an unstable product was obtained, 0.55 g (55%) of 2,4-diphenyl-3*H*-1,5-benzodiazepine-3-carboxylic acid (**5**), mp 200°; <sup>1</sup>H nmr (methanol-*d*<sub>4</sub>): δ 5.1 (s, 1H, 3-H), 6.61 (dd, 2H, 6-, 9-H, J = 5.9, 3.4 Hz), 7.13 (dd, 2H, 7-, 8-H, J = 5.9, 3.4 Hz), 7.56–7.61 (m, 4H, *o*-phenyl protons), 7.67–7.74 (6H, m, *m*, *p*-phenyl protons); ir (potassium bromide): 1420 (C=O), 1580 (C=N), 1640 (C=O), 3500 (OH) cm<sup>-1</sup>.

Diethyl (2,4-Diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonate (**6**).

A mixture of 3-bromo-2,4-diphenyl-3*H*-1,5-benzodiazepin (**4**) (3.75 g, 10 mmoles), diethyl malonate (1.5 ml, 10 mmoles) and sodium ethanolate (15 ml) (2.5 *M*) was heated at 60–65° for 24 hours. After cooling to room temperature, the reaction mixture was dried. Then, an adequate amount of water was added. After extraction by chloroform, the collected extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (1:1; v/v) to get 0.97 g (26%) of diethyl (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonate (**6**), mp 130°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.07 (t, 6H, 2CH<sub>3</sub>, J = 7.1 Hz), 3.17 (d, 1H, 3-H, J = 11.4 Hz), 4.03 (q, 4H, 2CH<sub>2</sub>, J = 7.1 Hz), 6.41 (d, 1H, -CH(COOEt)<sub>2</sub>, J = 11.4 Hz), 7.36–7.42 (m, 8H, *m*, *p*-phenyl protons and 6-, 9-H), 7.64 (dd, 2H, 7-, 8-H, J = 6.1, 3.4 Hz), 8.05 (m, 4H, *o*-phenyl protons); ms: (chemical ionization) m/z 455 (M+1), 294 (M<sup>+</sup> -CH(COOEt)<sub>2</sub>); ir (potassium bromide): 1580 (C=N), 1750 (C=O) cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.99; H, 5.77; N, 6.16; O, 14.08. Found: C, 74.20; H, 5.81; N, 6.27; O, 14.00.

(2,4-Diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonic Acid (**8**).

A mixture of diethyl (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonate (**6**) (0.60 g, 1.32 mmoles) and sodium ethanolate (5 ml) (2.5 moles of sodium in ethanol) was stirred at room temperature for 3 days. After evaporation of the solution, the residue was diluted with water then acidified until pH 5–6. The crude product was extracted by chloroform. The organic layer was evaporated. Recrystallization from chloroform gave 0.24 g (40%) of (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonic acid (**8**), mp 240°; <sup>1</sup>H nmr (methanol-*d*<sub>4</sub>): δ 2.91 (d, 1H, 3-H, J = 11.2 Hz), 6.35 (d, 1H, -CH(COOH)<sub>2</sub>, J = 11.2 Hz), 7.27 (dd, 2H, 6-, 9-H, J = 6.1, 3.4 Hz), 7.30–7.34 (m, 6H, *m*, *p*-phenyl protons), 7.55 (dd, 2H, 7-, 8-H, J = 6.1, 3.4 Hz), 8.01–8.06 (m, 4H, *o*-phenyl protons); ir (potassium bromide): 1580 (C=N), 1610 (C=O), 3380 (OH) cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.35; H, 4.55; N, 7.03; O, 16.06. Found: C, 57.48; H, 3.86; N, 5.36; O, 24.5. (1 Na<sub>2</sub>CO<sub>3</sub> + 1 H<sub>2</sub>O), confirmed by mass spectrometry.

Diethyl (2,4-Diphenyl-1,2,4,5-tetrahydro-3*H*-1,5-benzodiazepin-3-yl)malonate (**9**).

This compound was prepared by selective reduction with cyanoborohydride according to the procedure described by Ohkawa *et al* [8]. Diethyl (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl) malonate (**6**) (0.18 g, 0.4 mmole) was added under nitrogen atmosphere at 0° to the mixture of an ethanolic solution on green of bromocresol (0.05 g/l, 1.12 ml) and sodium cyanoborohydride (0.056 g, 0.88

mmole) in ethanol:tetrahydrofuran (1:1; v/v) (2.4 ml). Neutralisation was performed by addition of 2.4 *N* hydrochloric acid in ethanol until a yellow color persisted. After addition of 1.5 ml of water, the crude product was extracted by chloroform. The organic phase was evaporated to give 0.15 g (85%) of diethyl (2,4-diphenyl-1,2,4,5-tetrahydro-3*H*-1,5-benzodiazepin-3-yl)malonate (**9**), mp 192°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.20 (t, 6H, 2CH<sub>3</sub>, J = 7.1 Hz), 3.27 (d, 1H, -CH(COOEt)<sub>2</sub>, J = 3.1 Hz), 3.57 (ddd, 1H, 3-H, J = 6.5, 3.1 Hz), 4.06 (q, 4H, 2CH<sub>2</sub>, J = 7.1 Hz), 4.80 (br d, 2H, 2-, 4-H, J = 6.5 Hz), 6.48 (dd, 2H, 6-, 9-H, J = 5.8, 3.4 Hz), 6.65 (dd, 2H, 7-, 8-H, J = 5.8, 3.4 Hz), 7.26–7.39 (m, 6H, *m*, *p*-phenyl protons), 7.55 (br dd, 4H, *o*-phenyl protons); ms: (chemical ionization) m/z 459 (M+1), 299 (M<sup>+</sup> -CH(COOEt)<sub>2</sub>); ir (potassium bromide): 1310 (C-N), 1600 (NH), 1750 (C=O), 3460 (NH) cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.34; H, 6.59; N, 6.11; O, 13.96. Found: C, 73.23; H, 6.64; N, 6.03; O, 14.10.

2-(2,4-Diphenyl-3*H*-1,5-benzodiazepin-3-yl)-2-ethoxycarbonylmalonic Acid (**7**).

A mixture of diethyl (2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)malonate (**6**) (0.60 g, 1.32 mmoles) and sodium ethanolate (5 ml) (2.5 *M*) was stirred at room temperature for 1 day. After concentration the residue was diluted with water and acidified until pH 5–6. The crude product was extracted with chloroform. After removal of the solvent, the residue was chromatographed on a silica gel column with methanol:chloroform (2:8, v/v) to afford 0.12 g (20%) of 2-(2,4-diphenyl-3*H*-1,5-benzodiazepin-3-yl)-2-ethoxycarbonylmalonic acid (**7**), mp 100°; <sup>1</sup>H nmr (deuteriochloroform): δ 0.93 (t, 3H, CH<sub>3</sub>, J = 7.0 Hz), 3.10 (d, 1H, 3-H, J = 11.3 Hz), 3.86 (q, 2H, CH<sub>2</sub>, J = 7.0 Hz), 6.13 (d, 1H, -CH(COOH)(COOEt), J = 11.3 Hz), 7.21–7.35 (m, 8H, 6-, 9-H, phenyl protons), 7.52 (dd, 2H, 7-, 8-H, J = 6.0, 3.3), 7.92 (br d, 4H, *o*-phenyl protons); ir (potassium bromide): 1580 (C=N), 1610 (C=O), 3400 (OH) cm<sup>-1</sup>.

## REFERENCES AND NOTES

\* Correspondence and reprints: Max Cussac\*, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie - Université J. Fourier, 38706 La Tronche Cedex - France; Tel. / Fax 33 (0)4 76 63 71 13; E-mail Max.Cussac@ujf-grenoble.fr.

- [1] K. S. Atwal, J. L. Bergey, A. Hedberg and S. Moreland, *J. Med. Chem.*, **30**, 635 (1987).
- [2] M. Chaffman and R. N. Brogden, *Drugs*, **29**, 387 (1985).
- [3] J. D. Elliott, M. A. Lago, R. D. Cousins, A. Gao, J. D. Leber, K. F. Erhard, P. Nambi, N. A. Elshourbagy, C. Kumar, J. A. Lee, J. W. Bean, C. W. Debrosse, D. S. Eggleston, D. P. Brooks, G. Feuerstein, R. R. Ruffolo, J. Weinstock, J. G. Gleason, C. E. Peishoff and E. H. Ohlstein, *J. Med. Chem.*, **37**, 1553 (1994).
- [4] A. Doherty, *Drug Disc. Today*, **1**(2), 60 (1996).
- [5] M. Webb, J. E. Bird, E. C. K. Liu, P. M. Rose, R. Serafino, P. Stein and S. Moreland, *J. Pharmacol. Exp. Ther.*, **272**(3), 1124 (1995).
- [6] M. Clozel, V. Breu, K. Burri, J. M. Cassal, W. Fischli, G. A. Gray, G. Hirth, B. M. Loffler, M. Muller, W. Neidhart and H. Ramuz, *Nature*, **365**, 759 (1993).
- [7] R. P. Barnes, N. L. Drake and R. Mozing, *Org. Synth.*, **III**, 555 (1955).
- [8] S. Ohkawa, N. Fujii, K. Kato and M. Miyamoto, International Patent, 95, 29900 (1995).
- [9] W. Ried and E. König, *Liebigs Ann. Chem.*, **755**, 24 (1972).