The Synthesis of Substituted 1,5-Benzodiazepines

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The synthesis of some substituted 1,5-benzodiazepines are described. The route is based on the reaction between 1,4-phenylenediamine and its derivative with crotonic acid or methacrilic acid.

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Our group has synthesized, developed and studied pure, resolved (*R,R*)- and (*R,S*)-stereoisomers of radioiodinated 3-quinuclidinyl 4-iodobenzilate (4-IQNB), a potent *m*-AChR antagonist that is non-selective for receptor subtypes. Detailed *in vitro* and *in vivo* studies of the compound labled with [^{123}I] or [^{125}I] have been published [1-4]. In order to generate *m*-AChR radioligands with improved pharmacokinetics suitable for quantitation, we have developed a group of m1-selective AChR antagonists possessing lipophilicity lower than that of IQNB [5,6]. Most recently, on the basis of existing structure-activity relationships, we have designed and synthesized a m2-selective AChR antagonist, 5-[[4-[(4-diethylamino)butyl]-1-piperidinyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one [7].

Scheme 1

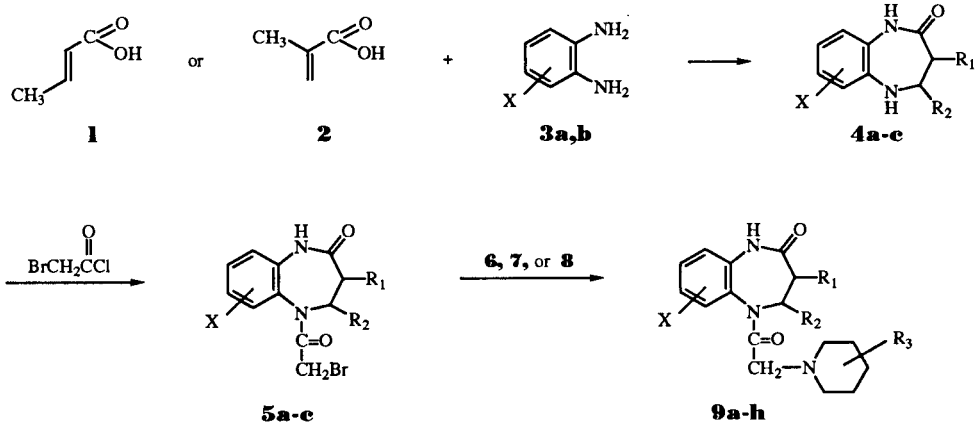
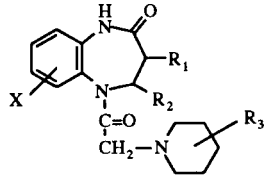


Table 1



Product	X	R_1	R_2	R_3	Yield (%)	Mp °C	Rf [a]
9a	H	H	CH_3	4-dimethylaminobutyl	61	137-138	0.46
9b	H	H	CH_3	4-diethylaminobutyl	68	117-119	0.46
9c	H	CH_3	H	4-dimethylaminobutyl	56	41-42	0.54
9d	H	CH_3	H	4-diethylaminobutyl	42	41-42	0.54
9e	H	CH_3	H	2-diethylaminomethyl	36	127-128	0.60
9f	8-Cl	H	CH_3	4-dimethylaminobutyl	48	162-163	0.48
9g	8-Cl	H	CH_3	4-diethylaminobutyl	56	146-147	0.55
9h	8-Cl	H	CH_3	2-diethylaminomethyl	32	95-96	0.70

[a] Methanol/ammonium hydroxide (98:2).

Table 2

NMR, IR, and Elemental Analytical Data on 5-[[2- or 4-[(Dialkylamino)methyl or butyl]-1-piperidinyl]-3 or 4-methyl or 8-Chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepines

Compound	^{1}H NMR: δ [a]	IR cm^{-1}	Formula	Elemental Analysis Calcd./Found C	H	N	Cl
9a	8.49 (b, 1H), 7.40 (td, J = 7.2, 1.4 Hz, 1H), 7.21 (m, 3H), 5.35 (m, 1H), 2.77 (m, 2H), 2.53 (d, J = 10.9 Hz, 1H), 2.39 (t, J = 5.5 Hz, 2H), 2.19 (m, 9H), 1.83 (q, J = 10.9 Hz, 2H), 1.46 (m, 4H), 1.12 (m, 10H)	1660-1700	$C_{23}H_{26}N_4O_2$	69.01 69.11	8.99 9.06	13.99 13.78	
9b	8.36 (b, 1H), 7.40 (m, 1H), 7.21 (m, 3H), 5.35 (m, 1H), 2.77 (m, 2H), 2.43 (m, 10H), 1.83 (q, J = 10.8 Hz, 2H), 1.46 (m, 4H), 1.10 (m, 16H)	1662-1682	$C_{25}H_{40}N_4O_2$	70.11 69.98	9.34 9.25	13.07 13.21	
9c	8.90 (b, 1H), 7.34 (m, 1H), 7.22 (m, 3H), 4.61 (t, J = 13.0 Hz, 1H), 3.56 (m, 1H), 2.83 (m, 4H), 2.54 (m, 1H), 2.21 (m, 8H), 1.83 (m, 2H), 1.48 (m, 4H), 1.08 (m, 10H)	1650-1700	$C_{23}H_{36}N_4O_2$	69.01 68.64	8.99 9.19	13.99 13.61	
9d	8.09 (b, 1H), 7.36 (m, 1H), 7.20 (m, 3H), 4.60 (m, 1H), 3.55 (m, 1H), 2.80 (m, 4H), 2.51 (m, 4H), 2.37 (m, 2H), 2.16 (m, 2H), 1.84 (m, 2H), 1.26 (m, 19H)	1670-1690	$C_{25}H_{40}N_4O_2$	70.11 69.63	9.34 9.36	13.07 13.27	
9e	7.81 (b, 1H), 7.23 (m, 4H), 4.58 (t, J = 13.1 Hz, 1H), 3.54 (m, 1H), 2.54 (m, 11H), 1.81 (m, 1H), 1.32 (m, 9H), 0.90 (t, J = 7.0 Hz, 6H)	1660-1682	$C_{22}H_{34}N_4O_2$	68.41 68.86	8.80 9.14	14.49 14.50	
9f	8.77 (b, 1H), 7.19 (m, 3H), 5.31 (m, 1H), 2.76 (m, 3H), 2.34 (m, 12H), 1.82 (m, 2H), 1.31 (m, 13H)	1670-1691	$C_{23}H_{35}ClN_4O_2$	63.54 63.17	8.05 8.09	12.88 12.68	8.15 8.45
9g	8.95 (b, 1H), 7.19 (m, 3H), 5.33 (m, 1H), 2.77 (m, 3H), 2.44 (m, 10H), 1.83 (m, 2H), 1.46 (m, 4H), 1.10 (m, 15H)	1665-1688	$C_{25}H_{39}ClN_4O_2$	64.89 64.57	8.42 8.45	12.10 11.91	7.66 7.72
9h	7.17 (m, 3H), 5.32 (m, 1H), 3.58 (d, J = 16.1 Hz, 1H), 2.79 (d, J = 16.1 Hz, 1H), 2.39 (m, 10H), 2.06 (m, 1H), 1.78 (b, 1H), 1.51 (m, 4H), 1.30 (m, 5H), 0.90 (t, J = 7.1 Hz, 6H)	1660-1690	$C_{22}H_{33}ClN_4O_2$	62.77 62.38	7.90 7.92	13.30 12.94	8.42 8.91

[a] The ^{1}H nmr spectra were obtained in deuteriochloroform solution.

This compound has been determined to be 10 times more potent at the m2 receptor than the reported most m2 selective antagonist, AQ-RA 741 [8]. The compound was not able to cross the blood-brain barrier in large quantity which may be due to its large size. Consequently, we decided to reduce the size of the tricycle and to prepare substituted 1,5-benzodiazepines.

We have synthesized as shown in Scheme I where crotonic acid (**1**) or methacrylic acid (**2**) react with 1,2-phenylenediamine or 4-chloro-1,2-phenylenediamine, **3a,b**, leading to tetrahydro-2*H*-1,5-benzodiazepin-2-ones **4**. Condensation of **4** with first bromoacetyl chloride followed by 2-diethylaminoethylpiperidine (**6**), 4-dimethylaminobutylpiperidine (**7**), or diethylaminobutylpiperidine (**8**) afford substituted 1,5-benzodiazepines **9**.

EXPERIMENTAL

The melting points were obtained on a Fisher-John apparatus. The ir spectra of the compounds, neat or in potassium bromide pellets, were obtained on a Perkin-Elmer 1710 Infrared Fourier Transform Spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC-300 instrument, and are expressed as parts per million (δ) from internal tetramethylsilane. Crotonic acid, methacrylic acid, 1,2-phenylenediamine, and 4-chloro-1,2-phenylenediamine were obtained from Aldrich.

4-Methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**4a**).

A mixture of 20.16 g (0.2 mole) of 1,2-phenylenediamine (**3a**), and 17.2 g (0.2 mole) crotonic acid (**1**) was poured into a 100 ml, 3-necked flask fitted with a stirrer, a condenser, and a thermometer. The reaction mixture was heated for 5 hours at 150-170°. The product was poured into water, and treated with sodium bicarbonate, and filtered. The product was purified by recrystallization from *n*-butanol. The yield of recrystallized compound melting at 189-190° amounts to 24 g (68%); tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.27; ir (potassium bromide): 1662 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 9.46 (b, 1H), 6.85 (m, 3H), 6.69 (m, 1H), 5.24 (d, J = 2.3 Hz, 1H), 3.82 (m, 1H), 2.44 (dd, J = 13.3, 4.0 Hz, 1H), 2.20 (dd, J = 13.3, 7.3 Hz, 1H), 1.18 (d, 6.3 Hz, 3H); ^{13}C nmr: δ 171.6, 139.4, 128.1, 124.4, 121.7, 120.3, 119.4, 53.2, 41.6, 23.2.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.00; H, 6.80; N, 15.72.

3-Methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**4b**).

This compound was prepared from 10.08 g (0.1 mole) of 1,2-phenylenediamine (**3a**), and 8.6 g (0.1 mole) of methacrylic acid (**2**) in the same manner as for **4a**. A solid was obtained which was recrystallized from *n*-butanol, yield 13.2 g (75%), mp 214-215°; tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.29; ir (potassium bromide): 1659 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 9.41 (b, 1H), 6.81 (m, 3H), 6.61 (m, 1H), 5.59 (d, J = 4.5 Hz, 1H), 3.39 (m, 1H), 3.17 (t, J = 10.8 Hz, 1H), 2.63 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.19; H, 6.84; N, 15.75.

8-Chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**4c**).

This compound was prepared from 14.26 g (0.1 mole) of 4-chloro-1,2-phenylenediamine (**3b**), and 8.6 g (0.1 mole) of crotonic acid (**1**) by the procedure described for the preparation of **4a**. The crude material consists of the mixture of the two isomers with chlorine in position 7 and 8. Its ^{13}C nmr indicates that the yield of 8-chloro-isomer is approximately twice that of 7-chloro-isomer. It was crystallized from *n*-butanol to give 12.85 g (61%) of the 8-chloro-isomer **4c**; mp 195-196°; tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.32; ir (potassium bromide): 1651 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.54 (b, 1H), 6.85 (m, 3H), 5.51 (d, J = 2.2 Hz, 1H), 3.79 (m, 1H), 2.46 (dd, J = 13.6, 3.4 Hz, 1H), 2.24 (dd, J = 13.6, 7.4 Hz, 1H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C nmr: δ 171.4, 138.3, 128.7, 123.8, 122.1, 121.1, 120.8, 52.4, 41.8, 23.1.

Anal. Calcd. for $C_{10}H_{11}ClN_2O$: C, 57.02; H, 5.26; Cl, 16.83; N, 13.30. Found: C, 56.93; H, 5.25; Cl, 16.97; N, 13.24.

We were not successful in obtaining the pure 7-chloro-derivative.

5-Bromoacetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**5a**).

The diazepinone **4a** (1.76 g, 0.01 mole), bromoacetyl chloride (2 ml), and *N,N*-dimethylaniline (0.8 g) in dry THF (30 ml), were stirred at room temperature for 2 days. After the solvent was removed, the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with 5% potassium bicarbonate, and dried over magnesium sulfate. After removal of the solvent, the residue was crystallized from *n*-butanol to give 1.6 g (54%), mp 169-170°; tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.27; ir (potassium bromide): 1670-1690 cm^{-1} (br); ^1H nmr (deuteriochloroform): δ 9.31 (b, 1H), 7.48 (m, 1H), 7.29 (m, 3H), 5.34 (m, 1H), 3.72 (m, 1H), 3.57 (m, 1H), 2.40 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; Br, 26.89; N, 9.43. Found: C, 48.62; H, 4.35; Br, 26.65; N, 9.31.

5-Bromoacetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**5b**).

This compound was prepared from 1.76 g (0.01 mole) of diazepinone **4b** and 2 ml of bromoacetyl chloride by the procedure described above for the preparation of **5a**. It was crystallized from *n*-butanol to give 1.82 g (61%) pure product, mp 157-159°; tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.39; ir (potassium bromide): 1665-1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.90 (b, 1H), 7.46 (m, 1H), 7.30 (m, 3H), 4.59 (m, 1H), 3.78 (m, 2H), 3.60 (m, 1H), 2.80 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; Br, 26.89; N, 9.43. Found: C, 48.57; H, 4.32; Br, 26.63; N, 9.32.

5-Bromoacetyl-8-chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**5c**).

This compound was prepared from 2.11 g (0.01 mole) of diazepinone **4c** and 2 ml of bromoacetyl chloride in the same manner as **5a**. A solid was obtained which was recrystallized from *n*-butanol, yield 2.25 g (68%), mp 202-204°; tlc (silica gel, hexane/ethyl acetate, 1:1) R_f 0.46; ir (potassium bromide): 1661, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.57 (b, 1H), 7.27 (m, 3H), 5.30 (m, 1H), 3.54 (m, 2H), 2.48 (m, 1H), 2.34 (m, 1H), 1.25 (d, J = 6.3 Hz, 3H).

Anal. Calcd. for $C_{12}H_{12}BrClN_2O_2$: C, 43.47; H, 3.65; Br, 24.10; Cl, 10.69; N, 8.45. Found: C, 43.81; H, 3.68; Br, 24.17; Cl, 10.71; N, 8.26.

Typical Procedure for the Preparation of 5-[[2- or 4-[(Dialkylamino)methyl or butyl]-1-piperidinyl]acetyl]-3 or 4-methyl or 8-Chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **9a-h** (Tables 1 and 2). 5-[[4-[4-(Dimethylamino)butyl]-1-piperidinyl]acetyl]-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**9a**).

The bromoacetyl derivative **5a** (1.48 g, 0.005 mole), 4-[4-(dimethylamino)butylpiperidine [7] (0.92 g, 0.005 mole), and potassium carbonate (0.42 g), were stirred at room temperature in 30 ml acetonitrile for one day. The solvent was evaporated to dryness. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The ethyl acetate was removed under reduced pressure and the residue crystallized from acetone-petroleum ether.

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