SYNTHESES OF FUNCTIONALIZED DERIVATIVES OF QUINAZOLINES AND 1,4-BENZODIAZEPINES

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Abstract - The 2-substituted 1,4-benzodiazepines (4 and 6) were synthesized. The reaction of 2-aminobenzophenone oximes with ethyl 4-chloroacetoacetate gave the 1,4-benzodiazepines (4) and the 1,2-dihydroquinazolines (5); the latter were treated with a base to result ring expansion giving the 1,4-benzodiazepines (6).

The 2-substituted 1,4-benzodiazepines were of interest as precursors for derivatives with an heterocyclic ring fused at the 1,2-bond. Tricyclic 1,4-benzodiazepines fused with a pyrrole, imidazole or triazole moiety have led to clinically useful derivatives such as midazolam, estazolam and triazolam[1-6]. We now report a direct synthesis of 1,4-benzodiazepin-2-ylideneacetate and the synthesis of functionalized 1,2-dihydroquinazolines which can be converted into the former by ring expansion. We found that ethyl 4-chloroacetoacetate 1 condensed with 2-aminobenzophenone oximes 2 or 3 to yield 2-substituted 1,4-benzodiazepines 4 or quinazolines 5 (Scheme 1). If the reaction was carried out with the syn isomer 2, the benzodiazepine compound 4 was mainly obtained and quinazoline compound 5 only in minor amounts, while with anti isomer 3, the quinazoline 5 was the major product (Table 1).

Previously a type of condensation between anti-2-amino-5-chlorobenzophenone oxime 3b and α-chloro aldehydes or α-chloro ketones was described but the formation of 1,4-benzodiazepines was not found[7-8]. Ethyl 4-bromoacetoacetate reacted with the condensed products of 2-aminobenzophenone oximes and acetone

Scheme 1

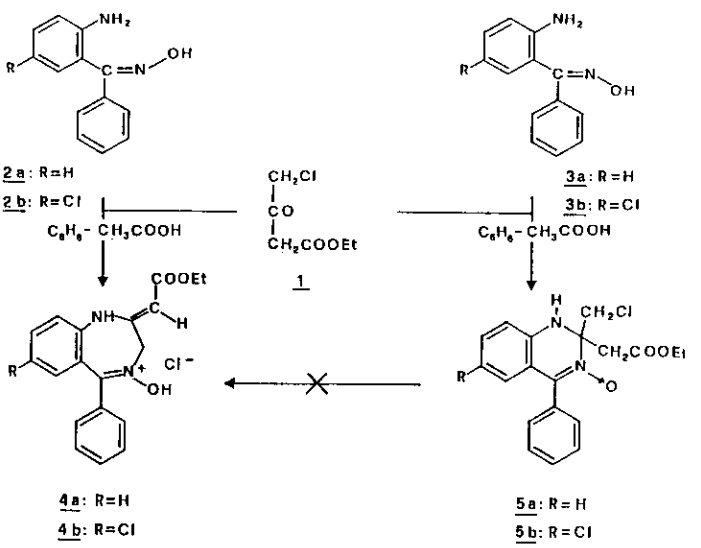


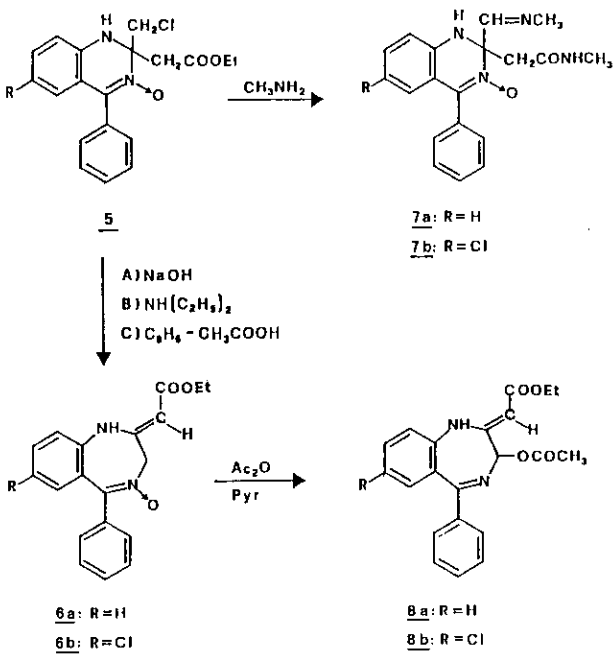
Table 1

Yields % of 1,4-benzodiazepines and quinazolines

R	oxime	mp °C	1,4-benzodiazepine	yield (%)	quinazoline	yield (%)
H	syn 2a	167	4a	64	5a	14
H	anti 3a	127	"	10	"	70
Cl	syn 2b	169	4b	69	5b	10
Cl	anti 3b	132	"	6	"	66

to afford 1,2-dihydro-2,2-disubstituted quinazolines[9]. In this instance the compounds with 1,4-benzodiazepine structure were obtained only by enlargment of the quinazoline ring. Prolonged heating of 5 in boiling benzene-glacial acetic acid (9:1) did not lead to 4 (Scheme 1) but to 1,4-benzodiazepine N_4-oxide 6 (Scheme 2). The same product was obtained when 5 was treated with a base such as sodium hydroxide or diethylamine, whereas the reaction of 5 with methylamine led only to the product derived from substitution of the halogen of the chloromethyl group by methylamine with subsequent dehydrogenation, and amide formation from the carbethoxy group 7[10-12]. The mechanism of reaction was not studied. The reaction of 6 with acetic anhydride in pyridine at room temperature resulted in a Polonovsky-type rearrangement to give the acetoxy compound 8 (Scheme 2).

Scheme 2



5

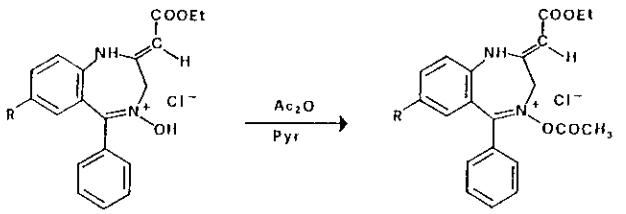
7a: R = H
7b: R = Cl

6a: R = H
6b: R = Cl

8a: R = H
8b: R = Cl

When 4 was treated with acetic anhydride in pyridine at room temperature, the O-acetyl derivative 9 was obtained as the sole isolated product (Scheme 3).

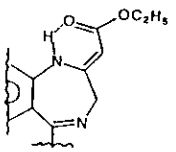
Scheme 3



4

9a: R=H
9b: R=Cl

To all the compounds with exocyclic double bond, the structure 10 with hydrogen bonding between the N_1-hydrogen atom and the carbonyl of the carbethoxy group[13] was assigned; the conjugated acetate carbonyl stretching appeared at 1660 cm^{-1} in the ir spectrum. The chemical shift of the vinylic proton at 5.0 ppm appeared as a sharp singlet in the nmr spectrum, whereas multiplet having an unresolved fine structure appearing at 4.2-4.8 ppm was assigned to the methylene protons of the benzodiazepine ring.



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EXPERIMENTAL

Melting points are determined in open capillaries on a Büchi apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240c Elemental Analyzer. Merck silica gel 60, 70-230 mesh, was used for column chromatography. Ir spectra were recorded in nujol mulls with a Perkin-Elmer mod. 397 spectrophotometer. ^1H and ^{13}C nmr spectra were recorded with a Varian XL 200 spectrometer for DMSO d-6 solution (TMS as internal standard): the values of chemical

shifts are expressed in ppm and coupling constants (J) in Hz. Fast Atom Bombardment mass spectra were recorded on a Kratos MS 80 spectrometer.

General procedure for the condensation of 2-aminobenzophenone oximes with ethyl 4-chloroacetoacetate.

A solution of ethyl 4-chloroacetoacetate (1.97 g, 12 mmol) in anhydrous benzene (10 ml) was added dropwise to a solution of the appropriate 2-aminobenzophenone oxime (10 mmol) in anhydrous benzene (90 ml) and glacial acetic acid (10 ml). The mixture was stirred at room temperature for 1 h and refluxed for an additional 1 h. After cooling, water was added and the mixture was neutralized with sodium hydrogen carbonate (sat.sol.). The organic layer was separated, washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded an orange thick oil which was chromatographed eluting with benzene-ethyl acetate (95:5) to yield 4 and then with ethyl acetate to yield 5. Recrystallization from suitable solvents gave analitycal samples.

2,3-Dihydro-2- [(ethoxycarbonyl)methylene] -4-hydroxy-5-phenyl-1H-1,4-benzodiazepinium chloride (4a).

Colorless needless from ethanol, mp 144°C. Ir : 3240,3140,1680 cm^{-1}. ^{1}H Nmr: 1.15 (t,3H,J=7.0,CH_2-CH_3), 4.01 (q,2H,J=7.1,CH_2-CH_3), 4.10-4.90 (broad m,2H,CH_2), 4.96 (s,1H,=CH), 7.07-7.46 (m,9H,Ar-H), 9.81 (s,1H,NH), 11.93 (s,1H,OH). ^{13}C Nmr 14.30 (CH_2-CH_3), 41.76 (CH_2), 58.60 (CH_2-CH_3), 89.22 (=CH), seven signals at 125.20, 125.37, 126.80 (2CH), 128.15 (2CH), 129.0, 129.17, 129.30 due to 9 CH aromatic groups and six signals at 129.67, 135.70, 136.82, 153.41, 155.27, 168.30 due to quaternary C atoms. Anal.Calcd for $C_{19}H_{19}ClN_2O_3$: C,63.59;H,5.34;N,7.80. Found: C,63.81;H,5.61;N,7.86. FAB-Ms (glycerol), m/z: 359 (M^++1).

7-Chloro-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-4-hydroxy-5-phenyl-1H-1,4-benzodiazepinium choride (4b).

White crystals from aqueous ethanol, mp 119-120°C. Ir: 3200,3140,1660 cm^{-1}. ^1H Nmr: 1.14 (t,3H,J=7.1,CH_2-$C\underline{H}_3$), 4.01 (q,2H,J=7.2,$C\underline{H}_2$-CH_3), 4.20-4.60 (broad m,2H,CH_2), 4.99 (s,1H,=CH), 7.16 (d,1H,J=1.8,CH-6), 7.29-7.50 (m,7H,Ar-H), 9.76 (s,1H,NH), 12.10 (s,1H,OH). Anal.Calcd for $C_{19}H_{18}Cl_2N_2O_3$: C,58.02;H,4.61;N,7.12. Found: C,58.29;H,4.63;N,7.02.

2-Chloromethyl-1,2-dihydro-2-[(ethoxycarbonyl)methyl]-4-phenylquinazoline-3-oxide (5a).

Yellow prisms from ethanol, mp 147-148°C. Ir: 3350,1750 cm^{-1}. ^1H Nmr: 1.04 (t,3H,J=7.0,CH_2-$C\underline{H}_3$), 2.74 and 3.23 (dd,2H,J=14.9,J=15.0,$C\underline{H}_2$-CO), 3.84 and 4.39 (dd,2H,J=11.4,J=11.4,$C\underline{H}_2$-Cl), 3.93 (q,2H,J=7.1,$C\underline{H}_2$-CH_3), 6.46-7.51 (m,9H,Ar-H), 7.37 (s,1H,NH). Anal.Calcd for $C_{19}H_{19}ClN_2O_3$: C,63.60;H,5.34;N,7.80. Found: C,63.45;H,5.40;N,7.61. FAB-Ms (glycerol), m/z: 359 (M^++1).

6-Chloro-2-chloromethyl-1,2-dihydro-2-[(ethoxycarbonyl)methyl]-4-phenylquinazoline-3-oxide (5b).

Yellow prisms from ethanol, mp 145°C. Ir: 3360,1750 cm^{-1}. ^1H Nmr: 1.06 (t,3H,J=7.0,CH_2-$C\underline{H}_3$), 2.75 and 3.29 (dd,2H,J=15.3,J=14.3,$C\underline{H}_2$-CO), 3.83 and 4.40 (dd,2H,J=11.5,J=11.4,$C\underline{H}_2$Cl), 3.96 (q,2H,J=7.2,$C\underline{H}_2$-CH_3) 6.34 (d,1H,J=2.3,CH-5), 6.72 (d,1H,J=8.6,CH-8), 7.10 (dd,1H,J=2.3,J=8.5,CH-7), 7.32-7.53 (m,5H,Ar-H), 7.67 (s,1H,NH). ^{13}C Nmr: 15.71 (CH_2-$\underline{C}H_3$), 42.60 ($\underline{C}H_2$-CO), 51.10 ($\underline{C}H_2$Cl), 62.22 ($\underline{C}H_2CH_3$), six signals at 116.43, 125.71, 130.41(2CH), 131.10, 131.29(2CH), 131.37 due to 8 CH groups and seven signals at 84.65, 118.34, 122.99, 132.31, 140.15, 142.29, 169.78 due to quaternary C atoms. Anal.Calcd for $C_{19}H_{18}Cl_2N_2O_3$: C,58.02;H,4.61;N,7.12. Found: C,57.93;H,4.66;N,7.05. FAB-Ms (glycerol), m/z: 394 (M^++1).

2,3-Dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepine-4-oxide (6a).

Method A.

A mixture of 2.3 ml of 2N sodium hydroxide and 25 ml of 1,2-dimethoxyethane was chilled to 0-5°C and 1.2 g (3 mmol) of 5a was added. After 30 min, 35 ml of water was added slowly, while keeping the temperature at 0-5°C. The precipitate so obtained was separated by filtration, washed with water and dried in vacuo over phosphorus pentoxide to give 1.0 g (yield 83%) of 6a. Recrystallization from cyclohexane gave colorless prisms melting at 154-155°C. Ir: 3200,1660 cm^{-1}. ^{1}H Nmr: 1.20 (t,3H,J=7.1,CH_2-$\underline{C}H_3$), 4.11 (q,2H,J=7.1,$\underline{C}H_2$-CH_3), 4.49-4.66 (broad m,2H,CH_2) 5.00 (s,1H,=CH), 6.90-7.51 (m,9H,Ar-H), 10.45 (s,1H,NH). ^{13}C Nmr: 14.27 (CH_2-$\underline{C}H_3$), 58.94 ($\underline{C}H_2$-CH_3), 66.29 ($\underline{C}H_2$), 87.52 (=CH), seven signals at 121.86,123.26,127.75 (2CH),129.10,130.10,130.32 (2CH),131.24 due to 9 CH aromatic groups and six signals at 124.91,133.65,138.50,140.92,153.39, 168.85 due to quaternary C atoms. Anal.Calcd for $C_{19}H_{18}N_2O_3$: C,70.77;H,5.63;N,8.69. Found: C,70.64;H,5.55;N,8.61. FAB-Ms (glycerol), m/z: 324 (M^++1).

Method B

To a solution of 0.9 g (2.5 mmol) of 5a in dry benzene (20 ml), 0.37 g (5 mmol) of diethylamine was added dropwise and the resultant mixture was refluxed for 16 h. The precipitate obtained after cooling was filtered, washed to neutrality with water and dried in vacuo over phosphorus pentoxide. The solid was recrystallized from benzene to give an analytical sample (mp 150°C, yield 50%) whose ir and ^{1}H Nmr spectral data and C,H,N analyses were consistent with the structure proposed for 6a.

Method C

A solution of 0.9 g (2.5 mmol) of 5a in a dry benzene-glacial acetic acid (9:1) (20 ml) was refluxed for 36 h. After cooling a little amount of water was added and the mixture was neutralized with sodium hydrogen carbonate.

The usual work up of the organic layer gave a residue which was chromatographed with chloroform-ethyl acetate (8:2) as eluent (yield 30%). A further chromatography on silica gel 60 F_{254} TLC plates, 20x20 cm, thickness 2 mm, gave an analytical sample identical with 6a.

7-Chloro-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepine-4-oxide (6b).

Prepared with the same procedure used for 6a, starting from 5a. White plates from benzene, yield 88%, mp 150°C. Ir: 3300, 1660 cm^{-1}. ^1H Nmr: 1.20 (t,3H,J=7.2,CH_2-CH_3), 4.10 (d,2H,J=7.1,CH_2-CH_3), 4.40-4.80 (broad m,2H,CH_2), 5.04 (s,1H,=CH), 6.84 (d,1H,J=2.0,CH-6), 7.35-7.53 (m,7H,Ar-H), 10.44 (s,1H,NH). ^{13}C Nmr: 14.24 (CH_2-CH_3), 59.00 (CH_2-CH_3), 66.37 (CH_2), 88.20 (=CH) six signal at 124.00,127.92 (2CH),129.35,129.73,129.94,130.24(2CH) due to 8 CH aromatic groups and seven signals at 126.37,126.93,133.21,137.63,140.00,152.75,168.66 due to quaternary C atoms. Anal.Calcd for $C_{19}H_{17}ClN_2O_3$: C,63.95;H,4.80;N,7.85. Found C,63.88;H,4.82;N,7.78. FAB-Ms (glycerol), m/z: 358 (M^++1).

1,2-Dihydro-2-N-methylacetamide-2-methylaminomethyl-4-phenylquinazoline-3-oxide (7a).

A suspension of 0.716 g (2 mmol) of 5a in 7 ml of methanolic methylamine (30%) was stirred at room temperature for 15 h. The solid product formed was filtered off and the solution was concentrated in vacuo. The residue was treated with ether and ice-cold aqueous dilute hydrochloric acid. The ether was discarded and the acidic aqueous solution was made alkaline with ice-cold sodium hydroxide. The reaction product was then extracted with methylene chloride, the organic layer was dried over sodium sulfate and evaporated in vacuo. The residue so obtained was chromatographed using ethyl acetate-methanol (1:1) as eluent

(yield 80%). A further chromatography gave an analytical sample as light brown flakes, mp 196-198°C (dec.). Ir 3610,3300,1660 cm^{-1}. ^1H Nmr: 1.93 (s,3H,CONHC<u>H</u>$_3$), 2.40 (dd,2H,J=17.0,J=17.4,C<u>H</u>$_2$-CO), 2.78 (s,3H,N-CH_3), 4.40 (s,1H,=CH), 6.59 (m,4H,3 Ar-H+Ar-NH), 7.02-7.56 (m,6H,Ar-H), 8.48 (s,1H,CO-NH). Anal.Calcd for $C_{19}H_{20}N_4O_2$: C,67.82;H,6.00;N,16.66. Found: C,67.50;H,5.78;N,16.74.

<u>6-Chloro-1,2-dihydro-2-N-methylacetamide-2-methyliminomethyl-4-phenylquinazoline-3-oxide</u> (<u>7b</u>).

The same synthetic procedures employed for compound <u>7a</u> were used to obtain <u>7b</u> in 80% yield, as white needles from ethyl acetate-isopropanol (1:1), mp 228-229°C. Ir: 3480,3330,3280,1680 cm^{-1}. ^1H Nmr: 1.95 (s,3H,CONHC<u>H</u>$_3$), 2.42 (dd,2H,J=17.3,J=16.9,C<u>H</u>$_2$-CO), 2.79 (s,3H,NCH_3), 4.41 (s,1H,=CH), 6.52 (d,1H,J=2.4,CH-5), 6.66 (d,1H,J=8.6,CH-8), 6.84 (s,1H,NH), 7.11 (dd,1H,J=2.4,J=8.5,CH-7), 7.37-7.58 (m,5H,Ar-H), 8.62 (s,1H,CONH). ^{13}C Nmr: 27.03 (CONHC<u>H</u>$_3$), 28.28 (N-CH_3), 78.10 (C<u>H</u>$_2$-CO), 118.29 (-CH=), six signals at 129.45(2CH), 130.06, 130.17, 131.50(2CH), 131.67, 133.33 due to 8 CH aromatic groups and seven signals at 90.41, 92.59, 121.54, 124.57, 137.70, 144.93, 171.02 due to quanternary C atoms. Anal.Calcd for $C_{19}H_{19}ClN_4O_2$: C,61.52;H,5.17;N,15.11. Found: C,61.19;H,5.20;N,15.20. FAB-Ms (glycerol), m/z: 372 (M^++1).

<u>3-Acetoxy-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepine</u> (<u>8a</u>).

0.22 g (1 mmol) of <u>6a</u> in a mixture of the 5-fold amount of acetic anhydride and the 5-fold amount of pyridine was stirred at room temperature overnight. The solution was then poured onto crushed ice. The precipitate so obtained was collected and washed carefully to neutrality, then dried in vacuo over phosphorus pentoxide (yield 70%). Colourless prisms from petroleum ether-cyclohexane (1:1), mp 124-125°C. Ir: 3275,1780,1680 cm^{-1}. ^1H Nmr 1.18 (t,3H,J=7.0,CH_2-C<u>H</u>$_3$), 2.30 (s,3H,COC<u>H</u>$_3$), 4.07 (q,2H,J=7.0,C<u>H</u>$_2$-CH_3), 4.98 (s,1H,=CH), 6.18 (s,1H,CH-3), 7.17-7.61 (m,9H,Ar-H), 10.38 (s,1H,NH). Anal.Calcd for $C_{21}H_{20}N_2O_4$: C,69.20;H,5.53;N,7.68. Found: C,69.08;H,5.50;N,7.55.

3-Acetoxy-7-chloro-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepine (8b).

Prepared with the same procedure used for 8a in 60% yield, as colourless needles from petroleum ether, mp 142-143°C. Ir: 3250,1755,1670 cm^{-1}. ^1H Nmr: 1.18 (t,3H,J=7.0,CH_2-CH_3), 2.24 (s,3H,CO-CH_3), 4.08 (q,2H,J=7.0,CH_2-CH_3), 5.00 (s,1H,=CH), 6.22 (s,1H,CH-3), 7.16 (d,1H,J=2.4,CH-6), 7.44-7.65 (m,7H,Ar-H), 10.36 (s,1H,NH). Anal.Calcd for $C_{21}H_{19}ClN_2O_4$: C,63.22;H,4.80;N,7.02. Found: C,63.12;H,4.68;N,7.12.

4-Acetoxy-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepinium chloride (9a).

Prepared with the same procedure used for 8a starting from 4a in 83% yield, as white needles from ethanol, mp 132-134°C. Ir: 3280,1800,1680 cm^{-1}. ^1H Nmr: 1.14 (t,3H,J=7.1,CH_2-CH_3), 2.15 (s,3H,CO-CH_3), 4.00 (q,2H,J=7.1,CH_2-CH_3), 4.20-4.60 (broad m,2H,CH_2), 5.02 (s,1H,=CH), 7.44-7.57 (m,9H,Ar-H), 9.83 (s,1H,NH). Anal.Calcd for $C_{21}H_{21}ClN_2O_4$: C,62.92;H,5.28;N,6.98. Found: C,63.07;H,5.30;N,6.96.

4-Acethoxy-7-chloro-2,3-dihydro-2-[(ethoxycarbonyl)methylene]-5-phenyl-1H-1,4-benzodiazepinium chloride (9b).

Prepared with the same procedure used for 8a starting from 4b in 78% yield, as colourless needles from ethanol, mp 135°C. Ir: 3250,1780,1660 cm^{-1}. ^1H Nmr: 1.13 (t,3H,J=7.1,CH_2-CH_3), 2.16 (s,3H,CO-CH_3), 4.00 (q,2H,J=7.1,CH_2-CH_3), 4.24-4.67 (broad m,2H,CH_2), 5.05 (s,1H,=CH), 7.35-7.65 (m,8H,Ar-H), 9.79 (s,1H,NH). Anal.Calcd for $C_{21}H_{20}Cl_2N_2O_4$: C,57.89;H,4.63;N,6.43. Found: C,58.05;H,4.70;N,6.49.

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