NOVEL FUSED-RING 1,4-BENZODIAZEPINES: SYNTHESIS OF [1,4]OXATHIANO[5,6-b][1,4]BENZODIAZEPIN-2-ONES

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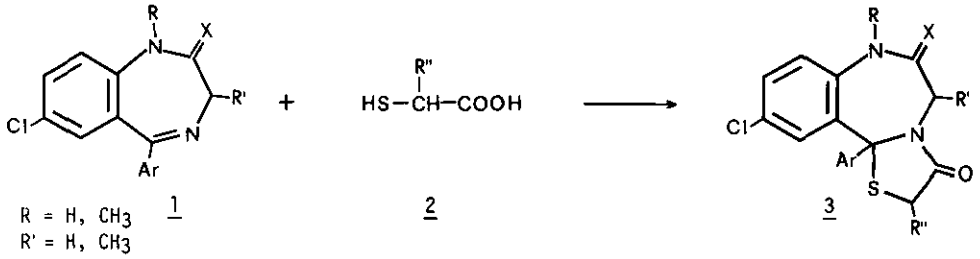
Abstract - The synthesis of the novel [1,4]oxathiano[5,6-b][1,4]benzodiazepin-2-ones was performed by condensation-cyclization reaction between 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one and mercaptocarboxylic acids. The structures of obtained compounds were assigned by means of spectroscopic measurements.

In the past decade considerable efforts have been devoted to the synthesis of functionalized benzodiazepine derivatives in order to obtain a more efficient pharmacological action and/or a more selective activity[1]. Quite promising results have been reached by the introduction in the benzodiazepine skeleton of a heterocyclic ring as pyrrole[2], pyrazole[3] or triazole[4] fused at the various edges of the heptatomic moiety. In connection with our investigation on the chemistry of benzodiazepine compounds[5] we have tested the reactivity of the C=N bond of benzodiazepine system towards different reagents as a tool for obtaining a valuable, facile cyclofunctionalization of the heptatomic nucleus[4,6].

The reaction of benzodiazepine derivatives 1 with mercaptocarboxylic acids 2 leads to 5,6,7,11b-tetrahydrothiazolo[3,2-d][1,4]benzodiazepin-3(2H)-ones 3 (Scheme 1)[7]. Compounds of this kind show interesting pharmacological action[7].

Scheme 1



R = H, CH_3 1
R' = H, CH_3
R" = H, CH_3
X = H_2, O

2

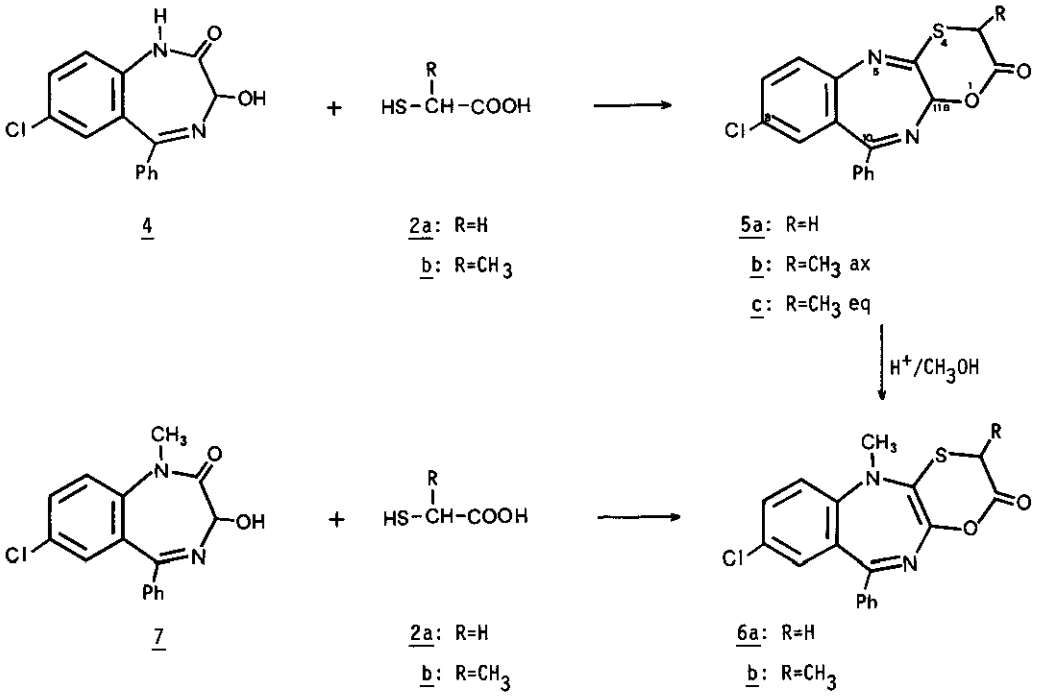
3

The presence of the hydroxyl group at position 3 of the heptatomic heterocyclic nucleus, as in 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one 4 (Oxazepam), induces a novel channel of reaction with mercaptocarboxylic acids, so allowing the possibility of a facile, different cyclofunctionalization route for the benzodiazepine system.

In this work we describe the synthesis of the new [1,4]oxathiano[5,6-b][1,4]benzodiazepin-2-one system obtained by direct one-pot reaction of mercaptocarboxylic acids with 3-hydroxyl-substituted 1,4-benzodiazepines.

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one 4 was allowed to react, in anhydrous benzene, with mercaptoacetic acid 2a under reflux for 30 min. The solvent was then evaporated in vacuo and the residue was repeatedly washed with water and recrystallized from ethanol to give the hitherto unknown 8-chloro-10-phenyl[1,4]oxathiano[5,6-b][1,4]benzodiazepin-2-one 5a in good yield (88%) (Scheme 2). Structure 5a was assigned to this product on the basis of spectroscopic data and was supported by satisfactory elemental analysis. The analytical data showed that the molecular formula is $C_{17}H_{11}ClN_2O_2S$ so indicating that the condensation between benzodiazepine and thioacid had occurred with elimination of two molecules of water. The ir spectrum exhibited a characteristic absorption maximum for the carbonyl stretching of oxathianone ring at 1790 cm^{-1}, while bands related to hydroxyl and amino group were absent.

Scheme 2



The ^1H nmr spectrum of 5a was compared to that of the starting 1,4-benzodiazepine 4. The signals of NH and OH groupings (10.85 and 6.39 ppm respectively in compound 4) were absent in derivative 5a; in addition the methine proton which appeared as a doublet (4.83 ppm, J=8.5 Hz) in 4 was shifted to low fields in 5a and resonated as a singlet (6.58 ppm). Furthermore, besides the aromatic protons, 5a showed a methylene proton resonance as an AB system (J=16.5 Hz) at 3.68 and 4.14 ppm. ^{13}C Nmr data also supported the attribution and are reported in Table 1.

Thus, both ir and nmr data confirm implicity of the proposed structure for the derivative 5a. However, the structure 5a was evidently confirmed mass spectrometrically. Beside the molecular ion at m/z 342, the interesting fragmentation at m/z 269 (100%) was observed, probably occurred by loss, from the molecular ion, of the radical $\cdot$S-CH=CO after a rearrangement through a 1,4-hydrogen shift[8].

By treatment of 5a with CH_3OH and H_2SO_4, the N-methyl derivative 6a was obtained with an isolated yield of 40%.

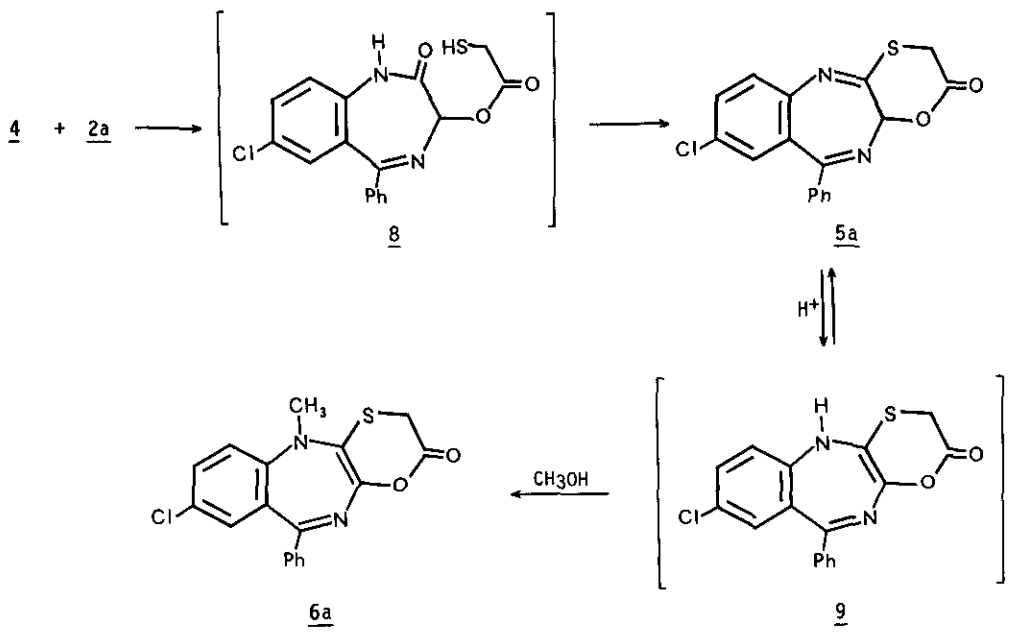
Structure 6a was assigned on the basis of elemental and spectroscopic analysis. Ir spectrum showed a carbonyl group at 1735 cm^{-1}; ^1H nmr spectrum gave the CH_3 singlet at 3.85 ppm, while the methine resonance at 6.58 ppm present in derivative 5a was absent. The A_2 pattern at 4.01 ppm, attributed to the methylene protons in the six-membered ring of compound 6a, was significantly different from the AB pattern present in 5a; this result, in agreement with the loss in 6a of the chiral centre present in derivative 5a at position 11a, can be explained in terms of a fast ring inversion of the system in solution.

A possible mode of formation of compounds 5a and 6a is shown in Scheme 3: this involves an initial esterification of the 3-OH to give the not isolated intermediate 8 which through acid promoted cyclization and subsequent removal of water, leads to the formation of 5a. Then, by reaction with H_2SO_4/CH_3OH the shift of the tautomeric imine-enamine equilibrium towards the enamine form 9 occurs, so allowing the N-methylation to give derivative 6a.

Table 1 - ^{13}C Nmr data of compounds 5a-c and 6a-b

Compd.	C-2	C-3	C-4a	C-5a	C-8	C-9a	C-10	C-11a	C-$\underline{C}H_3$	N-CH_3
5a	169.0	30.5	136.1	149.6	134.1	122.9	162.5	80.4		
5b	168.9	39.2	136.2	149.5	133.9	122.8	162.6	77.9	16.9	
5c	168.5	40.8	136.9	150.7	135.1	123.1	163.5	79.2	20.4	
6a	169.2	31.8	135.9	149.7	134.2	124.3	162.5	153.3		52.7
6b	169.4	41.2	135.5	149.8	132.0	125.0	160.1	156.9	17.6	52.9

Scheme 3



The reaction pathway has been tested with different substrates. Reaction of 4 with 2-mercaptopropionic acid 2b gave a mixture of two diastereoisomeric derivatives 5b and 5c in a relative ratio 50:50. The stereochemistry of these adducts has been established on the basis of spectroscopic data and confirmed by NOEDS experiments[9]. Derivative 5b showed the resonance of the methyl group as a doublet at 1.60 ppm, while C-H at position 3 resonated as a quartet (4.11 ppm) and C-H at position 11a as a singlet at 6.49 ppm. Irradiation of the resonance of H-11a gave positive enhancement for the signal of methyl group so suggesting a syn relationship between these protons with respect to the hexatomic ring. On the basis of these data and consideration of the chemical shift values, preferential conformation, which displays the methyl group axially situated in the boat shaped hexatomic ring[10], could be envisaged which accounts also for the downfield shift observed for H-3 with respect to the analogous proton in 5c. On the contrary, irradiation of H-11a in derivative 5c resulted in a positive NOE on the signal of the H-3. On the analogy of 5b, the preference for conformation which shows the methyl in pseudoequatorial position is supported by NOE experiments and by the downfield shift of CH_3 deshielded by the carbonyl cone.

Further reaction of diastereomeric 5b and 5c with H_2SO_4/CH_3OH afforded the N-methyl derivative 6b. Compounds 6a and 6b could also be obtained by directly reacting N-methyloxazepam 7 with mercaptocarboxylic acids (see Experimental) so allowing a different entry to this class of compounds.

EXPERIMENTAL

Melting points are determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were carried out on a C. Erba mod. 1106 Elemental Analyzer. Tlc was performed on Merck silica gel 60 F_{254} plates. For column chromatography Merck silica gel 60, 70-230 mesh, was used. Ir spectra were recorded in nujol on a Perkin Elmer mod. 257 spectrophotometer. ^1H and ^{13}C nmr spectra were observed at probe temperature on a Bruker WP 200 SY spectrometer in $CDCl_3$ (internal lock) with TMS as internal reference; chemical shifts are in ppm and coupling constants (J) in Hz. The proton NOE measurements were performed by the FT difference method on carefully degassed $CDCl_3$ solutions[9]. Mass spectra were recorded on a Hewlett Packard mod. 5995 A GC/MS. Oxazepam was extracted in Soxhlet with chloroform from the corresponding drug. N-Methyl-oxazepam (Temazepam) was synthesized according to the literature[11].

8-Chloro-10-phenyl[1,4]oxathiano[5,6-b][1,4]benzodiazepin-2-one (5a)

To a solution of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (4) (2.86g, 10 mmol) in anhydrous benzene (70 ml), mercaptoacetic acid (1.39ml, 20 mmol) was added and the mixture was refluxed for 30 min. After removal of the solvent in vacuo, an oily residue was obtained which, repeatedly washed with water and recrystallized from ethanol, gave a compound (yield 88%) with mp 152-154°C. Anal. calcd. for $C_{17}H_{11}ClN_2O_2S$: C, 59.54; H, 3.23; N, 8.16. Found: C, 59.33; H, 3.30; N, 8.01. MS m/z (%): 342 (M^+, 2), 269 (100), 241 (20), 205 (18), 163 (17), 77 (26). Ir: 1790 cm^{-1}. ^1H Nmr: 3.68 and 4.14 (dd, 2H, J=16, CH_2), 6.58 (s, 1H, H-11a), 7.40-8.08 (m, 8H, Ar-H).

8-Chloro-3-methyl-10-phenyl[1,4]oxathiano[5,6-b][1,4]benzodiazepin-2-ones (5b) and (5c).

2-Mercaptopropionic acid (1.77ml, 20 mmol) was added with stirring to a solution of compound 4 (2.86g, 10 mmol) in anhydrous benzene (70 ml) and the mixture was refluxed for 30 min. The solvent was then evaporated under reduced pressure and the obtained oily residue was washed repeatedly with water and recrystallized from ethanol to give a mixture of two isomers (yield 85%) which, subjected to column chromatography (CCl_4/EtOAc 8:2 as eluant), afforded the isomeric products 5b and 5c as stable adducts (relative ratio 50:50).

Data of 5b: mp 130-131°C. Anal. calcd. for $C_{18}H_{13}ClN_2O_2S$: C, 60.59; H, 3.67; N, 7.85. Found: C, 60.45; H, 3.71; N, 7.71. MS m/z (%): 356 (M^+, 7), 269 (100), 241 (18), 205 (14), 177 (13), 163 (18), 77 (39). Ir: 1770 cm^{-1}. ^1H Nmr: 1.60 (d, 3H, J=7.2, CH-CH_3), 4.41 (q, 1H, J=7.2, CH-CH_3), 6.49 (s, 1H, H-11a), 7.28-8.1 (m, 8H, Ar-H).

Data of 5c: mp 114-115°C. Anal. calcd. for $C_{18}H_{13}ClN_2O_2S$: C, 60.59; H, 3.67; N, 7.85. Found: C, 60.42; H, 3.78; N, 7.94. MS m/z (%): 356 (M^+, 6), 269 (100), 241 (19), 205 (19), 177 (11), 163 (13), 77 (42). Ir: 1780 cm^{-1}. ^1H Nmr: 1.71 (d, 3H, J=7.2, CH-CH_3), 4.09 (q, 1H, J=7.2, CH-CH_3), 6.59 (s, 1H, H-11a), 7.25-8.1 (m, 8H, Ar-H).

8-Chloro-2,5-dihydro-5-methyl-10-phenyl[1,4]oxathiino[5,6-b][1,4]benzodiazepin-2(3H)-one (6a)

To a stirred solution of compound 5a (1.02g, 3 mmol) in methanol (50 ml) was added dropwise 0.5 ml of conc. H_2SO_4. The resulting mixture was heated under reflux until tlc on silica gel (diethyl ether/light petroleum 8:2) indicated the disappearance of the starting material and subjected to chromatography on a column of silica gel using diethyl ether/light petroleum 8:2 as eluant. Recrystallization from diethyl ether gave 6a as colorless needles of mp 180-181°C (yield 40%). Compound 6a was *also obtained by reacting 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-*benzodiazepin-2-one 7 (3g, 10 mmol) and mercaptoacetic acid 2a (1.39 ml, 20 mmol) in anhydrous benzene (70 ml) under reflux; the optimum reaction time (3h) was determined by tlc monitoring, and was isolated (yield 25%) according to the above reported procedure. Anal. calcd. for $C_{18}H_{13}ClN_2O_2S$: C, 60.59; H, 3.67; N, 7.85. Found: C, 60.73; H, 3.75; N, 7.67. MS m/z (%): 356 (M^+, no peak), 298 (25), 240 (63), 239 (37), 177 (14), 77 (100). Ir: 1735 cm^{-1}. ^1H Nmr: 3.85 (s, 3H, N-CH_3), 4.01 (s, 2H, CH_2), 7.5-8.36 (m, 8H, Ar-H).

8-Chloro-2,5-dihydro-3,5-dimethyl-10-phenyl[1,4]oxathiino[5,6-b][1,4]benzodiazepin-2(3H)-one (6b)

Tha same synthetic procedures employed for compound 6a were used to obtain 6b, mp 120-122°C. Anal. calcd. for $C_{19}H_{15}ClN_2O_2S$: C, 61.54; H, 4.08; N, 7.55. Found: C, 61.68; H, 4.15; N, 7.39. MS m/z (%): 370 (M^+, no peak), 298 (38), 240 (82), 239 (56), 203 (57), 177 (22), 77 (100). Ir: 1738 cm^{-1}. ^1H Nmr: 1.81 (d, 3H, J=7.5, CH-CH_3), 3.88 (s, 3H, N-CH_3), 4.63 (q, 1H, J=7.5, C<u>H</u>-CH_3), 7.53-8.36 (m, 8H, Ar-H).

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