AN UNEXPECTED REACTION BETWEEN 2,3-DIHYDRO-2,2,4-TRIMETHYL-1H-1,5-BENZODIAZEPINE AND MERCAPTOACETIC ACID

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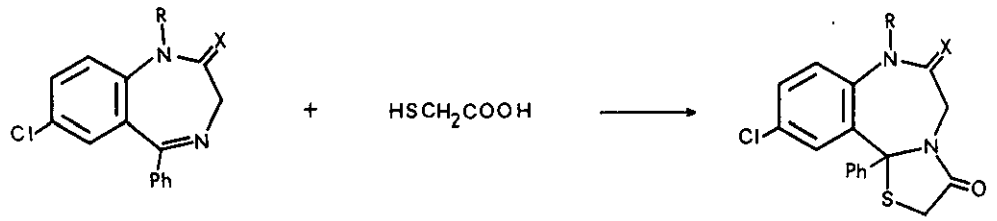
Abstract - The reaction of 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine with mercaptoacetic acid gave two unexpected main derivatives 2,3-dihydro-4-(2,3,4,5-tetrahydro-2,2-dimethyl-4-oxo-3-thienyl)-2,2-dimethyl-1H-1,5-benzodiazepine and 1,1-dimethyl-1H,3H-thiazolo[3,4-a]benzimidazole. The structures of obtained compounds have been assigned by means of spectroscopic measurements. A mechanism for their formation is also suggested.

Several benzodiazepine derivatives containing additional rings are compounds of pharmacological importance[1]. In connection with our investigation in the chemistry of the benzodiazepine system[2] with particular reference to its cyclofunctionalization and to the conformational characteristics of the newly synthesized compounds[3], we have extended the research to the study of the reactivity of the C=N bond in 1,4- and 1,5-benzodiazepine towards mercapto carboxylic acids.

The condensation-cyclization of derivatives 1 with mercaptoacetic acid 2 in boiling benzene affords 5,6,7,11b-tetrahydrothiazolo[3,2-d][1,4]benzodiazepin-3(2H)-ones 3 in satisfactory yields (50-60%)[4,5](Scheme 1). However, the same reaction, performed with 1,5-benzodiazepine 4 failed to give the expected cycloadduct 5.

Scheme 1

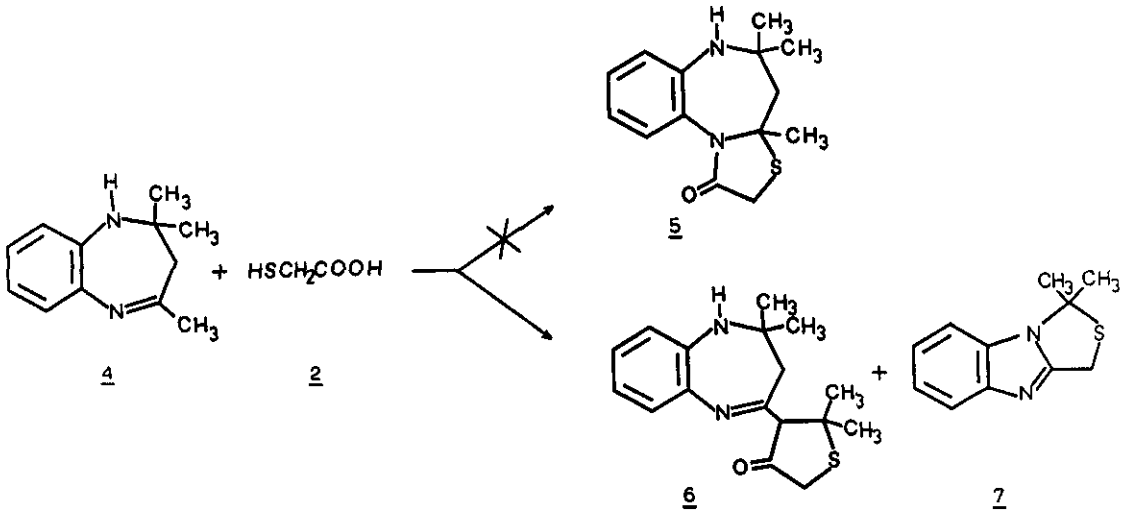


1 2 3

R = H, CH_3; X = H_2, O

We report here the isolation from this reaction of the adducts 6 and 7 (Scheme 2) and their identification as 2,3-dihydro-4-(2,3,4,5-tetrahydro-2,2-dimethyl-4-oxo-3-thienyl)-2,2-dimethyl-1H-1,5-benzodiazepine and 1,1-dimethyl-1H,3H-thiazolo[3,4-a] benzimidazole respectively.

Scheme 2



RESULTS

2,3-Dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine 4 reacted in anhydrous benzene with an excess of mercaptoacetic acid 2 under reflux for 24 h. The solvent was evaporated off and the reaction mixture was subjected to flash chromatography under slight pressure. The first eluted product 6 $C_{17}H_{22}N_2OS$ (m/z=302), was obtained as yellow prisms, mp 143-145°C, with an isolated yield of 28%. The structure was assigned on the basis of mass spectrometry, 'H nmr spectroscopy and supported by satisfactory elemental analysis.

The ir spectrum suggests the presence of a carbonyl group involved in a keto-enol equilibrium (1570 cm^{-1}); an additional band is present at 1605 cm^{-1} for the C=N stretching. The presence of a secondary amino group is inferred from the absorption at 3310 cm^{-1}.

The 'H nmr spectrum was compared with that of the starting 1,5-benzodiazepine derivative 4. The resonance of two methyl groups at C-2 (1.36 δ) is similar to the value of 4 (1.33 δ); on the contrary the resonance of the N=C-CH_3 moiety (2.33δ in 4) disappeared, while a single sharp peak is present at 1.7δ corresponding to two new geminal methyl groups on the pentatomic nucleus. Moreover the signal of methylene protons at C-3 appears at 2.61δ as a singlet; the second methylene group on the pentatomic nucleus is at lower field (3.6 δ) as a singlet. The magnetic equivalence of geminal methyl and methylene groups is indicative of a conformational mobility of compound 6 in solution at room temperature. This behaviour cannot be

ascribed to the more rigid tricyclic system of 3a,4,5,6-tetrahydrothiazolo[3,2-a][1,5]benzodiazepin-1(2H)-one 5. In fact, as reported[5], in 5,6,7,11b-tetrahydrothiazolo[3,2-d][1,4]benzodiazepin-3(2H)-ones 3 the methylene protons of heptatomic and pentatomic ring resonate as an AB system.

The methine proton of the pentatomic moiety is involved in a keto-enol tautomeric equilibrium: in solution this equilibrium is almost completely shifted towards the enolic form. This preference arises from the increased stability of the system as a consequence of the presence of a conjugate double bond system. In fact 'H nmr spectrum shows, for this proton, the presence of a broad signal, exchangeable with D_2O, at 2.75 δ, together with the NH resonance. The structure of compound 6 was confirmed unambiguously by X-ray diffraction analysis (shown below).

Further elution of the crude reaction mixture gave compound 7, $C_{11}H_{12}N_2S$, as white needles, mp 108-110°C, with a yield of 40%. The mass spectrum shows the molecular ion peak at m/z 204 so suggesting that some rearrangement had occurred. The 'H nmr spectrum shows, besides the aromatic protons in the range of 7.10-7.80 δ, a two proton singlet at 4.27 δ and a six proton singlet at 2.05 δ. The assigned structure was confirmed by alternative synthesis (shown below).

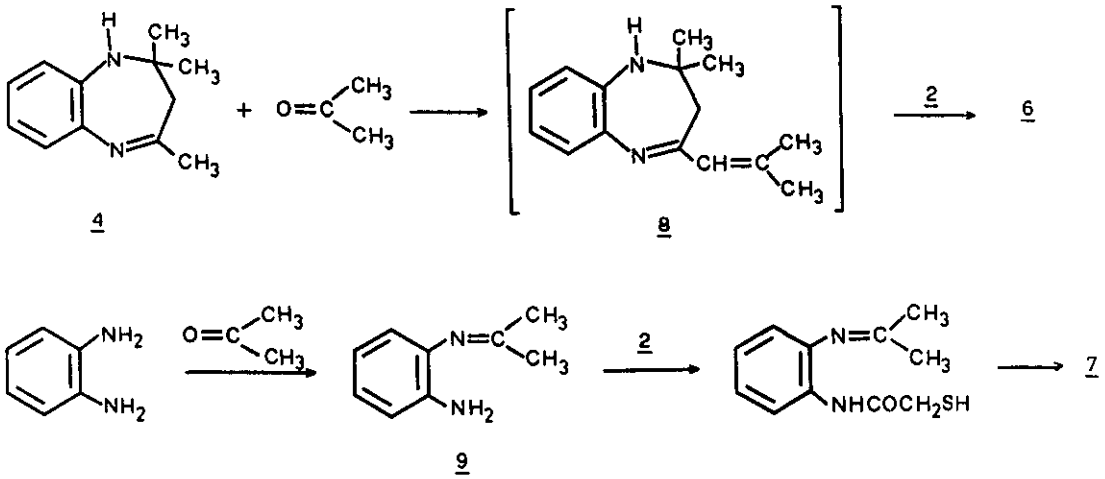
The formation of 6 and 7 may be rationalized as follows. The partial hydrolysis of starting 1,5-benzodiazepine 4 in the acid medium of the reaction, promoted by a catalytic amount of water, leads to the fission of the heptatomic ring which affords o-phenylenediamine and mesityl oxide. A retrograde aldol reaction gives acetone, which undergoes condensation with the unchanged 1,5-benzodiazepine to yield the proposed intermediate 8 (not isolated) (Scheme 3). Then the final product 6 is formed by cyclization of mercaptoacetic acid at the C=C bond.

From the o-phenylenediamine and acetone an alternative reaction pathway could be proposed: the obtained imino derivative 9, after reaction with mercaptoacetic acid at the amino group, undergoes intramolecular cyclization to the final product 7 (Scheme 3).

The proposed mechanism was supported by reacting directly o-phenylenediamine, acetone and mercaptoacetic acid[6]. After refluxing for 5 h in anhydrous benzene, the conventional work-up of the reaction mixture gave 1,1-dimethyl-1H,3H-thiazolo[3,4-a]benzimidazole in a very good yield (80%)[6]. Direct comparison with our obtained 7 proved the identity (mmp, glc, 'H nmr and ms).

In conclusion, the overall reaction pathway from the starting 1,5-benzodiazepine and mercaptoacetic acid could be rationalized on the basis of initial acid hydrolysis of the 1,5-benzodiazepine to acetone and o-phenylenediamine. The detection of small amount of o-phenylenediamine and acetone supports the proposed mechanism. Compound 5, an expected product was never detected.

Scheme 3



X-Ray crystal structure of compound 6 - An ORTEP prospective view of the molecule with the labelling of the atoms is shown in the Figure 1. Atomic fractional coordinates and their estimated standard deviations are in Table 1. Bond distances and selected bond and torsion angles are given in Tables 2-3.

The molecule 6 possesses a 1,5-benzodiazepine skeleton; the 4-carbon atom is linked to the tetrahydrothiophene ring. The presence of the intramolecular hydrogen bond involving the N1 of the heptatomic ring and the carbonyl oxygen, and the consequent extended delocalization of the conjugated double bond system are confirmed by the values of the bond distances (see Table 2).

The seven-membered ring assumes a boat conformation which can be described with respect to the least-square plane through the fused benzene ring: the displacements of N1 and N2 from this plane are -0.10 Å and -0.17 Å, while C5, C6 and C7 are out of the plane by 0.58, 1.49 and 0.82 Å respectively.

The five membered ring assumes an envelope conformation with the S atom as the flap

EXPERIMENTAL

Melting points were measured 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 60/F_{254} silica gel plates and column chromatography on Merck silica gel 60, 70-230 mesh. Ir spectra were determined in nujol on a Perkin Elmer mod. 257 spectrophotometer. 'H nmr spectra were recorded in $CDCl_3$ on a Brüker WP 80 SY with TMS as internal standard. Mass spectra were measured on a Hewlett Packard mod. 5995 GC/MS.

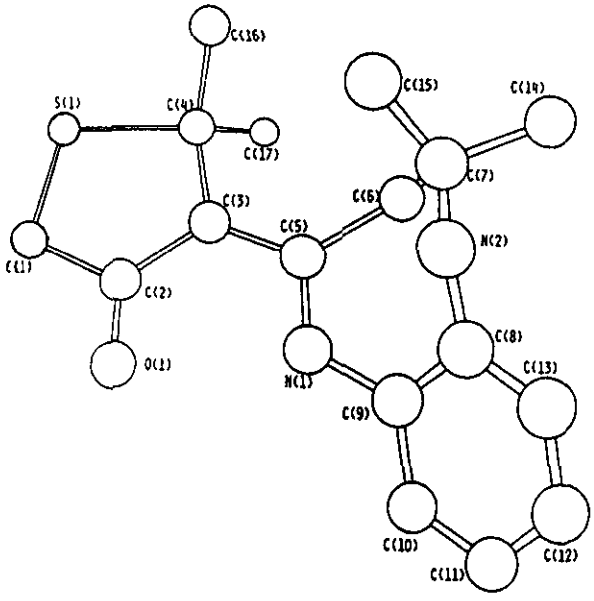


Figure 1-ORTEP drawing showing the atom-numbering scheme of molecule 6 (hydrogen atoms are omitted)

Table 3 - Some torsional angles

HN1-O1-C2-C3	167.09
C2-O1-HN1-N1	-10.20
C9-N1-C5-C3	174.37
C9-N1-C5-C6	-3.12
HN1-N1-C5-C3	1.71
HN1-N1-C5-C6	-175.77
C5-N1-C9-C8	46.75
HN1-N1-C9-C8	-140.93
HN1-N1-C9-C10	34.12
C5-N1-HN1-O1	-18.15
C9-N1-HN1-O1	168.60
C8-N2-C7-C6	32.40
C7-N2-C8-C9	-64.34
S1-C1-C2-O1	-177.24
O1-C2-C3-C4	177.10
O1-C2-C3-C5	1.75
C1-C2-C3-C4	0.0
C4-C3-C5-N1	-168.70
N1-C5-C6-C7	-68.56
C3-C5-C6-C7	114.13
C5-C6-C7-N2	50.88
N2-C8-C9-N1	2.70

2,3-Dihydro-4-(2,3,4,5-tetrahydro-2,2-dimethyl-4-oxo-3-thienyl)-2,2-dimethyl-1H-1,5-benzodiazepine (6) and 1,1-Dimethyl-1H,3H-thiazolo[3,4-a]benzimidazole (7)

To a solution of 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine 4 (1.5g, 8 mmol) in dry benzene (80 ml), mercaptoacetic acid (1.47g, 16 mmol) was added and the mixture was refluxed for 24 h. The solvent was evaporated off under reduced pressure, and the oily residue obtained, after neutralization with a 2% sodium carbonate, was subjected to flash chromatography on a column of silica gel using light petroleum - diethyl ether (8:2) as eluant. First elution gave 2,3-dihydro-4-(2,3,4,5-tetrahydro-2,2-dimethyl-4-oxo-3-thienyl)-2,2-dimethyl-1H-1,5-benzodiazepine 6, a yellow compound melting at 143-145°C after crystallization from diethyl ether (yield 28%). Anal. calcd. for $C_{17}H_{22}N_2OS$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.68; H, 7.30; N, 9.35. MS m/z (%): 302 (M^+, 22), 287 (19), 213 (8), 179 (23), 173 (9), 133 (100). ^{1}H nmr ($CDCl_3$) : 1.36 (s, 6H, heptatomic ring CH_3), 1.70 (s, 6H, pentatomic ring CH_3), 2.61 (s, 2H, heptatomic ring CH_2), 3.6 (s, 2H, pentatomic ring CH_2), δ6.51-7.03 (m, 4H, Ar-H).

Further elution gave 1,1-dimethyl-1H,3H-thiazolo[3,4-a]benzimidazole 7 as white needles, mp 108-110°C after crystallization from diethyl ether (yield 40%). Anal. calcd. for $C_{11}H_{22}N_2S$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.82; H, 5.96; N, 13.65. MS m/z (%): 204 (M^+, 65), 189 (56), 171 (78), 143 (15), 131 (100), 102 (19). ^{1}H nmr ($CDCl_3$) : 2.05 (s, 6H, CH_3), 4.27 (s, 2H, CH_2), 7.10-7.80 (m, 4H, Ar-H).

Table 1 - Atomic fractional coordinates ($x10^{-4}$) for non hydrogen atoms, with e.s.d.s. in the least significant digits in parentheses, for compound 6

	X/A	Y/B	Z/C		X/A	Y/B	Z/C
S1	3599(3)	5271(2)	250(2)	C8	3366(5)	8781(6)	5675(6)
O1	4252(3)	4978(4)	3778(4)	C9	4130(5)	8015(5)	5440(5)
N1	4004(4)	7183(4)	4433(4)	C10	5007(5)	7985(6)	6246(6)
N2	2432(4)	8715(5)	4949(5)	C11	5148(6)	8695(7)	7299(7)
C1	4001(6)	4487(7)	1622(6)	C12	4401(6)	9472(7)	7541(7)
C2	3957(4)	5340(6)	2694(5)	C13	3534(6)	9509(6)	6732(7)
C3	3608(4)	6526(5)	2347(5)	C14	2121(9)	10382(9)	3420(9)
C4	3344(5)	6726(6)	945(5)	C15	1399(7)	8316(13)	3003(10)
C5	3599(4)	7418(5)	3255(6)	C16	2249(6)	6993(8)	491(7)
C6	3205(4)	8675(6)	3026(5)	C17	4020(7)	7684(9)	446(8)
C7	2292(5)	9012(6)	3611(6)				

Table 2 - Bond lengths and angles

S1	C1	1.743	C9	C10	1.379		N1	C5	C6	115.16
O1	C2	1.254	C10	C11	1.379		C3	C5	C6	125.34
O1	HN1	1.747	C11	C12	1.392		C5	C6	C7	116.94
N1	C5	1.344	C12	C13	1.370		N2	Ø7	C6	111.19
N1	C9	1.422	C2	O1	HN1	99.12	N2	C7	C14	110.25
N1	HN1	0.966	C5	N1	C9	126.52	C6	C7	C14	107.46
N2	C7	1.477	C5	N1	HN1	113.95	N2	C7	C15	107.18
N2	C8	1.402	C9	N1	HN1	119.13	N6	C7	C15	110.65
C1	C2	1.508	C7	N2	C8	121.12	C14	C7	C15	110.14
C2	C3	1.428	S1	C1	C2	107.86	N2	C8	C9	129.71
C3	C4	1.530	O1	C2	C1	118.87	N2	C8	C13	121.25
C3	C5	1.398	O1	C2	C3	126.18	C9	C8	C13	117.66
C4	C16	1.537	C1	C2	C3	114.89	N1	C9	C8	121.64
C4	C17	1.558	C2	C3	C4	114.61	N1	C9	C10	117.94
C5	C6	1.499	C2	C3	C5	119.99	C8	C9	C10	120.24
C6	C7	1.533	C4	C3	C5	125.22	C9	C10	C11	121.03
C7	C14	1.543	C3	C4	C16	114.97	C10	C11	C12	119.56
C7	C15	1.512	C3	C4	C17	112.41	C11	C12	C13	119.29
C8	C9	1.400	C16	C4	C17	111.14	C8	C13	C12	122.21
C8	C13	1.395	N1	C5	C3	119.44	O1	HN1	N1	138.43

Crystal data: $C_{17}H_{22}N_2OS$ Crystallizes in the monoclinic system, space group $P2_1/a$; a=13.712(2), b=11.063(2), c=10.880(2) Å; ß=98.6(1)°; V=1631.9 Å^3; Z=4; Dc=1.23 gcm^{-3}. 3024 (2873 Unique R=0.04) reflections were read on Philips PW 1100 diffractometer ϑ-2 mode up to 2ϑ=50°, using MoKα graphite monochromated radiation (λ=0.7107 Å). The structure was solved with Multan 80[7], and refined by block-diagonal least-squares. The thermal parameters were anisotropic for all non-hydrogen atoms. The hydrogen atoms were located on a difference Fourier map and refined isotropically.
The final R and Rw (w=1) factors for the 1294 reflections with $I \geq 3\sigma(I)$ considered observed was 0.0655.

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