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CYCLOADDITION REACTIONS OF 1,3-BENZOTHIAZINES V.[1] SYNTHESIS OF NEW TETRACYCLIC RING SYSTEMS[2]

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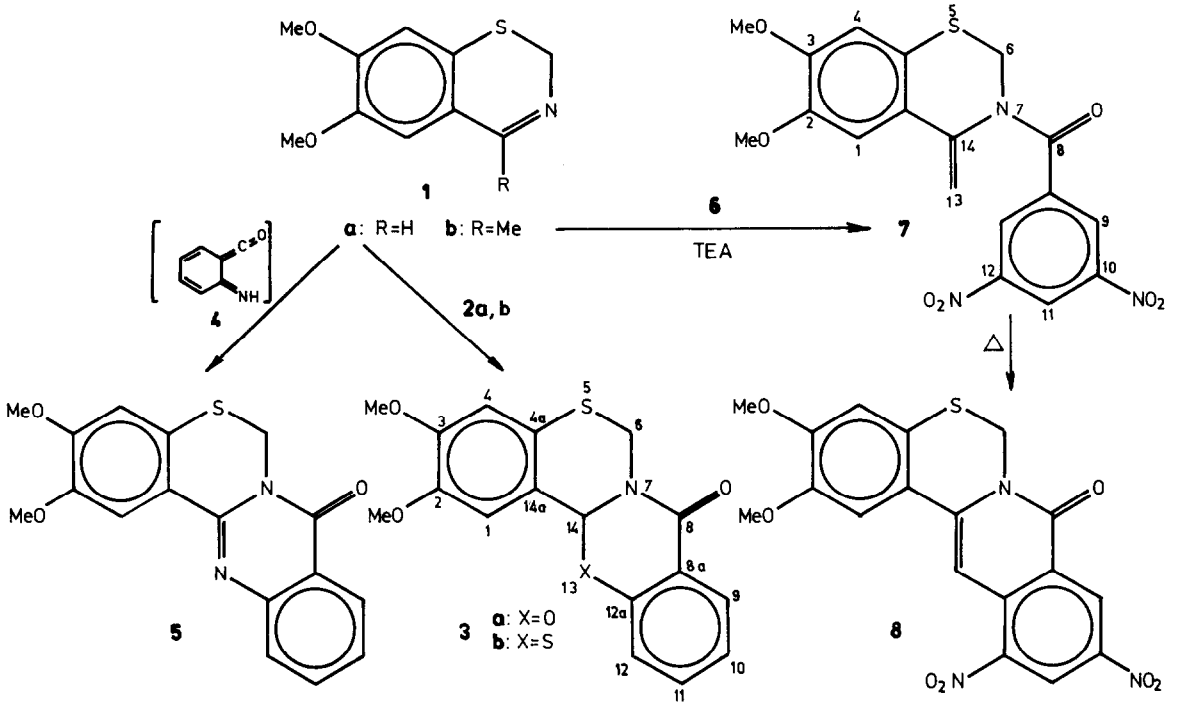
ABSTRACT: New tetracyclic derivatives (3a,b, 5, 8) similar to protoberberines, but containing a lactam structural element and other hetero atoms besides the bridgehead nitrogen in rings B and C, were prepared by cycloaddition of 6,7-dimethoxy-2H-1,3-benzothiazine (1a) with o-substituted aromatic carboxylic acid derivatives (2a,b, 4), and from 4-methyl-6,7-dimethoxy-2H-1,3-benzothiazine (1b) with 3,5-dinitrobenzoyl chloride.

Cyclic imines are easily acylated with acyl halides or anhydrides, and the resulting adducts may be used in the synthesis of heterocyclic compounds.[3-6] Treatment of salicyl chloride (2a)[7] or thiosalicyl chloride (2b) (prepared from salicylic acid or thiosalicylic acid and oxalyl chloride) with 6,7-dimethoxy-2H-1,3-benzothiazine (1a)[8] afforded the corresponding 1,3-benzoxazin-4-one (3a, 83%, mp 175-176 °C) or 1,3-benzothiazin-4-ones (3b, 77%, mp 175-176 °C).

Heating anthranilic acid with thionyl chloride produced an unstable sulfinamide anhydride,[9,10] which was treated with 6,7-dimethoxy-2H-1,3-benzothiazine (1a) in dry benzene at room temperature. In this reaction, via cycloaddition of an iminoketene-type intermediate followed by spontaneous dehydrogenation, compound 5 (69%, mp 255-257 °C) was formed. N-Aroylenamine-type enamines containing an electron-deficient aromatic ring undergo facile thermal cyclization to give the corresponding lactams.[11] Acylation of 4-methyl-6,7-dimethoxy-2H-1,3-benzothiazine (1b)[8] with 3,5-dinitrobenzoyl chloride (6) in the presence of TEA yielded the enamide 7 (89%, mp 159-161 °C), which was thermally cyclized upon refluxing in benzene to afford 8 (94%, mp 259-261 °C).

All spectroscopic data (Tables 1 and 2) are in full agreement with the postulated structures. The amide-I IR band appears between 1670 and 1640 cm^{-1}. The singlet of the isolated H-14 atom appears in the spectra of 3a,b and is missing from that of 5. Instead of this signal, the H-13 line is present in the spectrum of 8, considerably shifted downfield due to the anisotropy of the coplanar nitro group.[12a] The H-4 singlet is not sensitive to structural changes far from this hydrogen, while H-1 is more shielded in 3b than in 3a and in 8, and is strongly deshielded in 5, lying near the lone pair of N-13 in the same plane.[12b] The H-9,



10, 11 and 12 shifts show the expected values, considering the substituents on C-12a, and in the case of 8 on C-10 and 12 too.

The 6-methylene protons are equivalent in 5 and 8, proving the planar structure of the ring skeleton. These hydrogens in compounds 3a,b are non-equivalent; the shift-difference is small for 3a and significantly larger for 3b (0.18 and 1.50 ppm, respectively). This behaviour can very probably be explained by the different conformations of the two flexible heterorings.

Compound 3a has a preferred conformation, with the thiazine ring in a near-boat form, in which the dihedral angles of the C_6-H_a or C_6-H_e and C=O bonds are about 85 ° and 25°, and the distance between the tetrasubstituted benzene ring and H-6a is ∿ 3.8 Å (Fig. 1).

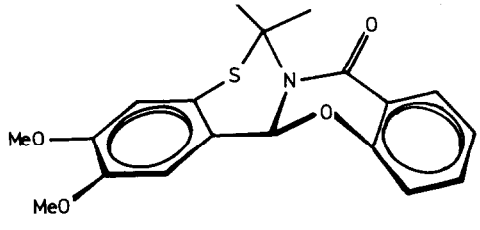


Fig.1.

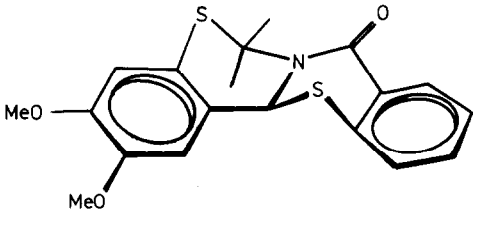


Fig.2.

By inversion of the thiazine ring, 3b takes on another form (Fig. 2), which dominates in the conformational equilibrium; in this, the 6-methylene protons mutually change their positions and H-6e is coplanar with the carbonyl group (the C_{6e}-H, C=O dihedral angle is ca. 0°). At the same time, the dihedral angle of the C_{6a}-H and C=O bonds is about 105°. This position lead to a significantly increased shielding of H-6a and a large opposite effect on H-6e, due to the anisotropy of the carbonyl group.[12c] Consequently, instead of the close lines of an

TABLE 1. IR (KBr, cm^{-1}) and ^1H NMR data ($CDCl_3$, δ_{TMS} = 0 ppm) at 250 MHz for compounds 3a,b, 5 and 8.

Compound	Amide-I band (IR)	H-6(2H) ax.	H-6(2H) eq.	H-14[a] s(1H)	H-1 s(1H)	H-4 s(1H)	H-9 dd(1H)	H-10 dt(1H)	H-11 dt(1H)	H-12 dd(1H)	OCH_3 s(3H)	OCH_3 s(3H)
3a	1668	4.82[b]	5.00[b]	6.18	7.10	6.80	7.96	7.14	7.47	7.06	3.84	3.88
3b	1641	4.26[c]	5.75[c]	6.26	6.88	6.85	8.14	≈7.30[d]	7.40	≈7.32[d]	3.88	3.90
5	1668	5.43[e]		-	7.98	6.83	8.30	7.45	≈7.75[d]	7.75[d]	3.95	4.03
8[f]	1670	5.35[e]		7.65	7.20	6.87	9.15[g]	-	9.50[g]	-	3.95	3.99

[a]H-13 for 8. [b]AB multiplet, J_{AB} = 12.6 Hz. [c]AX multiplet, J_{AX} = 12.6 Hz. [d]overlapping signals. [e]s(2H). [f]at 60 MHz, NO_2 bands: 1565, 1340, 835 cm^{-1}. [g]d, $J^m \approx 2$ Hz.

TABLE 2. ^{13}C NMR data (δ_{TMS} = 0 ppm) for compounds 3a,b and 5 in $CDCl_3$ at 20.14 MHz.

Compound	3a	3b	5
C-6	41.8	43.5	42.1
C-14	84.0	61.1	152.6
C-14a	126.2	126.9	120.6
C-1, 4	112.0[a]	112.6 112.7	110.4 113.0
C-2, 3	148.1 150.0	148.2 149.6	147.9 148.7
C-4a	123.0	122.2	122.9
C-8	161.5	163.6	160.5
C-8a	118.2	128.3	128.9
C-9	128.7	131.1	127.8
C-10	122.7	126.8	127.3
C-11	134.4	132.0	134.5
C-12	116.5	126.2	126.5
C-12a	157.0	137.3	148.5
OCH_3	56.0 56.3	56.1 56.3	56.4[a]

[a]two overlapping lines

AB multiplet as for 3a, for 3b an AX multiplet appears with an appreciable distance between the A and X doublets.

Both presumed conformers have a flat skeleton, and by assuming the arrangement illustrated in Fig. 2, 3b can avoid the steric hindrance between H-1 and the sulfur atom (this effect is smaller in 3a, due to the smaller atomic radius of the oxygen).

The structures of 3a,b, 5 and 8 are confirmed by the ^{13}C NMR shifts: The signals of the methylene carbon C-6, the C-8 carbonyl, the two methoxy-substituted atoms C-2 and 3, other quaternary C-14a, 4a, 8a and 12a and the protonated aromatic carbons C-1, 4, 9, 10, 11 and 12 are identifiable in the expected shift-regions. C-14 is more shielded in 3b than in 3a, as a consequence of the different α-effects of the sulfur and oxygen atoms.[12d] This signal appears at 152.6 ppm, in the interval characteristic of azomethine carbons.[12e]

The fact that no significant differences are observable in the shifts of the skeletal carbons (especially in the shifts of C-14, 14a and 1) suggests that the butterfly-wing-like form having the oxazinone or thioxazinone ring in the inverse with H-14 in the quasi-equatorial position plays only an unimportant role in the conformational equilibrium (the other inverse of this ring, with a quasi-axial H-14, is present in the postulated conformers). Such a structure should cause shielding on C-14, 14a and 1, due to a steric compression shift.[13]

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