HETEROCYCLES, Vol. 26, No. 9, 1987

SYNTHESIS OF 5-OXA-13-THIAPROTOBERBERINE DERIVATIVES[1]

János Szabó*, Gábor Bernáth, and +Pál Sohár

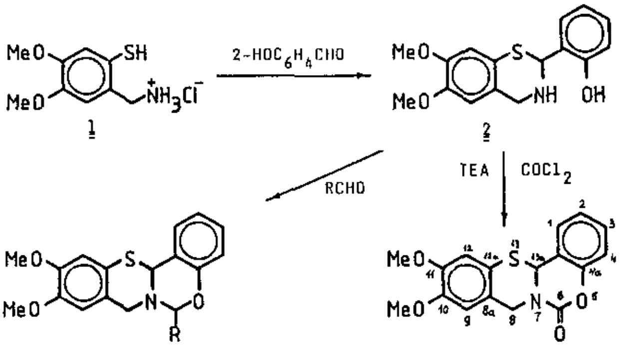
Institute of Pharmaceutical Chemistry, University Medical
School, Szeged, POB 121, H-6701 Szeged, Hungary
+Spectroscopic Department, EGIS Pharmaceuticals, POB 100,
H-1475 Budapest, Hungary

Abstract - With phosgene or aliphatic aldehydes, 6,7-dimethoxy-2-(2-hydroxyphenyl)-3,4-dihydro-2H-1,3-benzothiazine afforded novel 10,11-dimethoxy-6H,8H,13aH[1,3]benzoxazino[4,3-b][1,3]benzothiazine derivatives, members of a new heterocyclic ring system.

Through the reaction of 6,7-dimethoxy-2H-1,3-benzothiazine and salicyloyl chloride, we earlier synthesized 2,3-dimethoxy-6H,8H,13aH[1,3]benzothiazino[4,3-b][1,3]benzoxazin-8-one, the first representative of a novel heterocyclic system.[2] In the course of our work with the aim of the synthesis of further protoberberine derivatives, we sought a synthetic route to 5-oxa-13-thiaprotoberberines. In these hitherto unknown heterocycles, the carbon atoms in positions 5 and 13 on the protoberberine skeleton are substituted by hetero atoms.

6,7-Dimethoxy-2-(2-hydroxyphenyl)-3,4-dihydro-2H-1,3-benzothiazine (2) seemed to be an appropriate starting material for the synthesis of the target molecules. Compound 2 was synthesized by the condensation of 4,5-dimethoxy-2-mercaptobenzylammonium chloride and salicylaldehyde in an analogous way to the method[3] elaborated for the synthesis of this family of compounds. On the reaction of 2 with phosgene in benzene in the presence of triethylamine, 10,11-dimethoxy-6H,8H,13aH[1,3]benzoxazine [4,3-b][1,3]benzothiazin-6-one (3) was obtained.

Condensation of the dihydro-1,3-benzothiazine derivative 2 with aliphatic aldehydes in ethanolic solution gave the 6-unsubstituted (4a), or the corresponding 6-alkyl-10,11-dimethoxy-6H,8H,13aH[1,3]benzoxazino[4,3-b][1,3]benzothiazine derivatives (4b-d). The structures of the novel compounds were determined by elemental analysis plus ir, ^{1}H and ^{13}C nmr spectroscopy. Spectral data supporting structure 2 are as follows. The AB-type multiplet (2xd) of the methylene protons in the ^{1}H nmr spectrum confirm their non-equivalence (Table 1), indicating the cyclic structure. The incorporation of the o-hydroxyphenyl moiety is proved by the appearance of the sig-



4a: R = H; b: R = Me; c: R = Et; d: R = Pr

nals of the four aromatic protons in the ^{1}H, and those of the six carbon atoms in the ^{13}C nmr spectrum (Table 2). The characteristic downfield signals of the methine group between the two hetero atoms in the ^{1}H and ^{13}C nmr spectra can also be identified (5.75, and 61.7 ppm, respectively). The sharp νNH and diffuse (phenolic) νOH ir bands appear at 3255 and between 3200 and 2400 cm^{-1}, respectively.

Table 1. ^{1}H nmr data (chemical shifts in ppm, δ_{TMS} = 0 ppm and coupling constants in Hz) on compounds 2, 3 and 4a–d in CDCl$_3$ solution at 250.15 MHz

Compound	OCH$_3$ 2xs (2x3H)		NCH$_2$ Pos.8 (2H)^{a}		H-13a s (1H)	H-9,12 2xs (2x1H)		ArH-1,2,3,4 m (4H)	H-6	R(Pos.6)
2	3.82	3.86	3.99	4.18	5.57	6.51	6.60	6.8–7.4		–
3	3.84	3.87	4.48	5.38	6.17	6.56	6.67	6.9–7.5		–
4a	3.82	3.83	3.90	4.53	5.86	6.53	6.57	6.9–7.3	4.63^{a} 5.02^{a}	–
4b	3.81	3.84	4.14	4.32	6.05	6.50	6.56	6.9–7.3	5.06^{b}	1.54 d^{c}
4c	3.82	3.85	4.12	4.32	6.06	6.50	6.56	6.9–7.3	4.93^{d}	1.11 t^{c}, 1.85^{e}
4d	3.82	3.85	4.14	4.32	6.05	6.51	6.57	6.9–7.3	4.96^{d}	0.96 t^{c}, 1.4–1.9^{e}

[a] AB-type spectrum (2xd), J(A,B): 16.5–17.0 Hz; for compound 4a J(A,B) is 7.5 Hz for the methylene group in Pos.6; [b] qa (J: 5.6 Hz); [c] CH$_3$ (J: 7.2–7.5 Hz); [d] dd (J: 6.1 and 3.5 Hz); [e] CH$_2$, m, 2H (4a), 4H (4d).

Structure 3 is supported by the absence of νOH and νNH ir bands, and by the appearance of the νC=O band of the urethane moiety at 1730 cm^{-1} in the ir spectrum and the corresponding carbonyl line in the ^{13}C nmr spectrum (149.6 ppm). The 0.60 ppm downfield shift of the H-13a singlet relative to that for 2 is further supporting evidence for structure 3. The AB-type multiplet of the 8-methylene group and the significant downfield shift (0.49, and 1.20 ppm, respectively) of both doublets (mainly that which corresponds to the hydrogen coplanar with the carbonyl bond)

Table 2. ^{13}C nmr chemical shifts for compounds **2**, **3** and **4a**-**d** in $CDCl_3$ solution at 20.15 MHz[a] (δ_{TMS} = 0 ppm)

Compound	C-1[b]	C-2	C-3[b]	C-4a	C-5	C-13b	C-6	C-8	C-8a	C-9,12	C-10,11	C-12a	C-13a	OMe
2[c]	128.3	119.6	130.1	117.1	157.0	119.6	-	46.5	122.5	111.4	147.5 148.9	122.5	61.7	56.3
3	126.0	124.7	130.6	116.7	149.0[d]	117.0	149.6[d]	48.2	123.0	111.1 111.6	148.1 148.9	120.4	59.7	56.2 56.3
4a	126.9	120.7	129.2	116.7	152.4	119.4	77.5	52.1	123.9	110.6 111.5	147.0 148.7	121.6	62.9	55.9 56.1
4b	126.3	120.5	129.1	116.6	152.6	118.6	81.5	51.0	125.1	110.5 111.7	146.7 149.0	122.0	64.3	55.9 56.2
4c	126.0	120.1	128.8	116.4	152.5	118.5	84.7	50.5	124.7	110.2 111.5	146.5 148.7	121.6	64.3	55.6 55.9
4d	126.5	120.6	129.3	116.9	153.0	119.1	84.5	51.0	125.3	110.6 111.9	146.9 149.2	122.0	64.8	56.1 56.4

Signals of R: Me 18.5 (**4b**); Me 7.6, CH_2 24.4 (**4c**); Me 14.1, CH_2 17.2[e], 34.0. [a] In the case of **3** at 62.89 MHz; [b,d] Reversed assignments may also be possible; [c] All signals are broadened (the line pairs C-2,13b, C-9,12 and OMe in Pos. 10, and 11 are coalesced) due to hindered rotation about the C-13a, C-13b axis; [e] $\underline{C}H_2CH_3$ group.

relative to those for **2**, due to the -I and anisotropic effects of the carbonyl group,[4] are also indicative of structure **3**.

As evidence of structures **4a**-**d**, the ir νOH and νNH bands are absent, while the ^1H and ^{13}C nmr signals of the substituents R can be identified. The characteristic downfield shift of the ^{13}C nmr line at around 80 ppm of the 6-methine carbon between the oxygen and nitrogen atoms, the non-equivalence of the 8-methylene protons (AB multiplet), the downfield singlet of H-13a at around 6 ppm, and the corresponding carbon resonance at around 64 ppm, are decisive proof of the structure.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were run on an NIC 7199 FT-IR/GC spectrometer, in KBr pellets. ^1H and ^{13}C nmr spectra were recorded at 250.13 (^1H), and 62.89 or 20.14 (^{13}C) MHz, respectively, at room temperature in $CDCl_3$ solution on a Bruker WM 250 or a WP-80 SY FT spectrometer controlled by an ASPECT 2000 computer, in 5 or 10 mm tubes, using TMS as internal reference.

6,7-Dimethoxy-2-(2-hydroxyphenyl)-3,4-dihydro-2H-1,3-benzothiazine (**2**). - To 1.17 g (5 mmol) of 4,5-dimethoxy-2-mercaptobenzylammonium chloride suspended in 20 ml of ethanol, 0.61 g (5 mmol) of salicylaldehyde and 0.3 g of K_2CO_3 dissolved in 2 ml of water were added. After standing for 30 min, the precipitated crystals were collected by filtration (1.8 g; 83.8%). On recrystallisation from benzene, colourless needles were obtained, m.p. 157-158 °C.

$C_{16}H_{17}NO_3S$ (303.4) Calcd. C 63.34 H 5.65 N 4.62; Found C 63.28 H 5.53 N. 4.42.

10,11-Dimethoxy-6H,8H,13aH[1,3]benzoxazino[4,3-b][1,3]benzothiazin-6-one (3). - 1.52 g (5 mmol) of compound 2 in 20 ml of benzene, 0.50 g (5 mmol) of phosgene in 2.5 ml of toluene and 1.01 g (10 mmol) of triethylamine were mixed at room temperature during 1 h. The precipitated triethylammonium chloride was removed by filtration, the solution was evaporated and the residue was crystallized from ethanol to give colourless prisms (0.74 g; 45%), mp 200-201 °C. Anal. calcd. for $C_{17}H_{15}NO_4S$ (329.4): C 61.99 H 4.59 N 4.25. Found C 61.80 H 4.70 N 4.50.

General Procedure for Preparation of 4a-d. - To 0.61 g (2 mmol) of compound 2, 20 ml of ethanol and 5 mmol of the corresponding aldehyde were added, and the mixture was stirred for 2 h. The precipitated crystals were filtered off and recrystallized from ethanol to give the colourless compounds 4a-d (cf. Table 3).

Table 3. Physical and analytical data on compounds 4a-d

Compound	Yield %	Mp °C	Formula (Mol. weight)	Analysis/% Calcd./Found C	H	N
4a	80.6	158-159	$C_{17}H_{17}NO_3S$	64.74	5.44	4.44
			(315.4)	64.58	5.70	4.64
4b	92	169-170	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25
			(329.4)	65.50	5.79	4.56
4c	83.9	130-131	$C_{19}H_{21}NO_3S$	66.44	6.16	4.08
			(343.4)	66.61	6.46	4.37
4d	85.1	160-161	$C_{20}H_{23}NO_3S$	67.20	6.49	3.92
			(357.4)	66.99	6.72	4.23

ACKNOWLEDGEMENT

Thanks are due to Dr. S. Holly (Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Budapest) for recording the ir spectra.

REFERENCES AND NOTES

1. This paper is regarded as part 129 of the series: Saturated Heterocycles. Part 128: P. Sohár, G. Stájer, and G. Bernáth, Magn. Reson. Chem., submitted for publication.
2. L. Fodor, J. Szabó, G. Bernáth, and P. Sohár, Tetrahedron Lett., 1984, 25, 2013.
3. J. Szabó, I. Varga, E. Vinkler, and É. Barthos, Acta Chim. Acad. Sci. Hung., 1972, 72, 213.
4. P. Sohár, Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida, 1983, Vol. 1, pp. 32, 33 and Vol. 2, p. 132.

Received, 30th March, 1987