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

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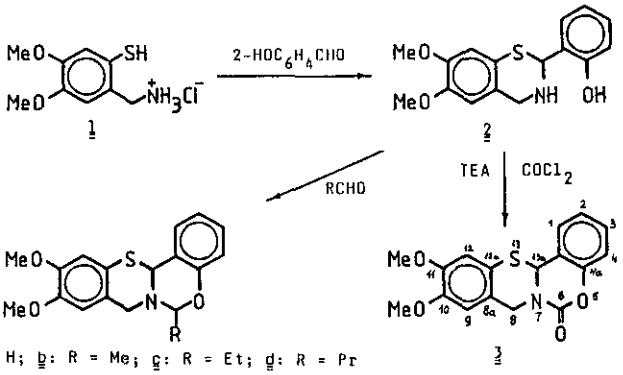
Abstract - With phosgene or aliphatic aldehydes, 6,7-dimethoxy-2-(2-hydroxyphenyl)-3,4-dihydro-2H-1,3-benzothiazine afforded novel 10,11-dimethoxy-6H,8H,13aH[1,3]benzoxazino[4,3-b][1,3]benzothiazine derivatives, members of a new heterocyclic ring system.

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-



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2

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

3

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	OCH_3 (2x3H)	NCH_2 Pos.8	NCH_2 (2H)[a]	H-13a s (1H)	H-9,12 2xs	H-9,12 (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] CH_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 ϑOH and ϑNH 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	$C_{17}H_{17}NO_3S$ (315.4)	64.74 64.58	5.44 5.70	4.44 4.64
4b	92	169-170	$C_{18}H_{19}NO_3S$ (329.4)	65.63 65.50	5.81 5.79	4.25 4.56
4c	83.9	130-131	$C_{19}H_{21}NO_3S$ (343.4)	66.44 66.61	6.16 6.46	4.08 4.37
4d	85.1	160-161	$C_{20}H_{23}NO_3S$ (357.4)	67.20 66.99	6.49 6.72	3.92 4.23

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REFERENCES AND NOTES

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