SYNTHESIS OF 2,2'-ETHYLENE-BIS(1,2-DIHYDROBENZO[h]-3H-4,2-BENZOXAZINE) AND 3,3'-ETHYLENE-BIS(3,4-DIHYDROBENZO[h]-2H-1,3-BENZOXAZINE) AND ASSIGNATION OF THEIR ^{1}H-NMR SPECTRA USING THE LAOCN3 COMPUTER PROGRAM

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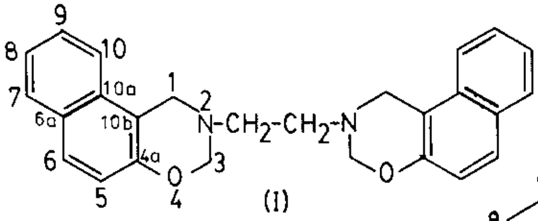
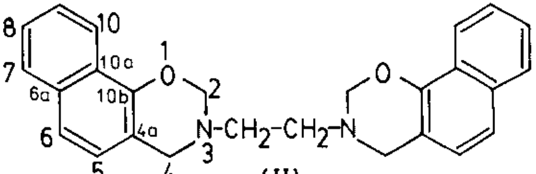
Abstract- Two new bis-benzoxazines, 2,2'-ethylene-bis(1,2-dihydrobenzo[h]-3H-4,2-benzoxazine) (I) and 3,3'-ethylene-bis(3,4-dihydrobenzo[h]-2H-1,3-benzoxazine) (II) were obtained by the Mannich reaction of β and α-naphthol with formaldehyde and ethylendiamine. Their ^{1}H-nmr spectra were simulated and interpretated using the LAOCN3 computer program.

We recently have synthesized some bis-benzoxazines because similar compounds have shown antimicrobial activity against gram-positive bacteria, being better than several common antibiotics such as ampicillin, tetracycline and chloramphenicol[1,2].



(I)



(II)

Betti and co-workers[3,4] as well as Burke et al[5,6] have reported the synthesis of related compounds by the Mannich reaction of β and α-naphthol with aldehydes and ammonia or a primary amine in a molar ratio of 1:2:1 to yield m-naphthoxazines.

We modified this type of general reaction in order to obtain bis-benzobenzoxazines. Compounds I and II were obtained by treatement of β or α-naphthol with ethylendiamine and formaldehyde in a molar ratio of 2:1:4.

Up to date compounds I and II are not described in the Chemical Literature.

DISCUSSION

The structures of compounds I and II were established completely using spectroscopic methods. Full assignment of ^{13}C-nmr spectra was done by means of theoretical calculations, "off resonance" spectra and by analogy with data reported for similar substances[7].

The methylene proton of both compounds were assigned confronting the theoretical chemical shifts calculated using Shoolery's rule[8] with the experimental data.

In the ^{1}H-nmr spectra, aromatic protons showed two spin-spin coupling systems. One of them was a simple AB system. The other one was a complex splitting pattern of four interacting protons and the spectra became second order. Rather than blind trial and error fitting of experimental complex spectra to chemical shifts and coupling constants, it would be preferable to have a computer program that would calculate a set of shifts and couplings which produced a best fit of experimental data to theoretical parameters. In our interpretation of these complex splitting patterns we used the LAOCN3 computer program, which is undoubtedly the most widely used[9], in order to calculate the best parameter set. After several simulations and iterations we could plot out computer spectra ostensibly equal with the experimental ones and the protons were then assigned without any doubt. Root mean square (RMS) error for compound (I) was 0.048 and 0.198 for (II).

EXPERIMENTAL

GENERAL PROCEDURE

A mixture of methanol (50ml) and formaldehyde 37% (3.2ml), cooled in an ice bath, was stirred for 10 min and ethylendiamine (0.6g) was then added slowly dropwise. After 5 min a solution of β-naphthol (2.8g) in methanol (10ml) was added and the reaction mixture was left at room temperature for 10 min. A white solid compound that precipitated after this time was separated by vacuum filtration and purified by column chromatography.

A similar method was employed to make the synthesis of compound II.
^{1}H-nmr spectra were determined with a Varian EM-390 instrument, ^{13}C-nmr spectra with a Varian XL-100-A-FT-16K instrument, ms spectra with a Shimadsu 9020 spectrometer, mp's were recorded with a Busch SMP-20 hot-stage apparatus, TLC and CC were performed on silica gel detecting with iodine and Draggendorff reagent.

2,2'-Ethylene-bis(1,2-dihydrobenzo[h]-3H-4,2-benzoxazine) (I). Is a crystalline solid, mp 189-190°C, insoluble in the most of common organic solvents; lightly soluble in chloroform. The yield of the reaction was 90%. ms spectra (70 eV) m/z (%): 396 (M^{+},2.0), 240(7.6), 198(4.6), 156(48.6), 128(100.0), 42(41.6); ^{1}H-nmr spectra (90 MHz, $CDCl_3$): δ 3.09 (s,4H,R-CH_2-N), 4.37 (s,4H,Ar-CH_2-N), 5.05 (s,4H,O-CH_2-N), 7.02 (d,2H,H-C5,$\underline{J}$=8.85Hz), 7.34($\underline{A}$BCD-system,2H,H-C9,$\underline{J}_{AB}$=6.96,$\underline{J}_{AC}$=0.92,$\underline{J}_{AD}$=8.11Hz), 7.46 (A$\underline{B}$CD-system,2H,H-C8,$\underline{J}_{AB}$=6.96,$\underline{J}_{BC}$=8.36,$\underline{J}_{BD}$=1.26Hz), 7.58 (AB$\underline{C}$D-system,2H,H-C7, $\underline{J}_{AC}$=0.92,$\underline{J}_{BC}$=8.36,$\underline{J}_{CD}$=0.04Hz), 7.63 (d,2H,H-C6,$\underline{J}$=8.85Hz), 7.75 (ABC$\underline{D}$-system,2H,H-C10, $\underline{J}_{AD}$=8.11,$\underline{J}_{BD}$=1.26,$\underline{J}_{CD}$=0.04Hz); ^{13}C-nmr spectra (50.4 MHz, $CDCl_3$): δ 48.0 (R-CH_2-N), 50.4 (1), 82.4 (3), 111.5 (10b), 118.4 (5), 120.8 (10), 123.3 (8), 126.3 (9), 127.9 (7), 128.4 (6), 128.8 (10a), 131.7 (6a), 151.7 (4a).

3,3'-Ethylene-bis(3,4-dihydrobenzo[h]-2H-1,3-benzoxazine) (II). Precipitated as crystalline needles; it is unstable to light and heat; mp 135-136°C (decomposition); it is soluble in ether, chloroform, ethyl acetate, acetone, benzene and toluene. The yield was 50%. ms spectra (20 eV) m/z (%): 396 (M^{+},4.4), 240(18.0), 198(2.7), 156 (100.0), 128(37.3), 42(6.9); ^{1}H-nmr spectra (90 MHz, $CDCl_3$): δ 3.07 (s,4H,R-CH_2-N), 4.12 (s,4H,Ar-CH_2-N), 5.07 (s,4H,O-CH_2-N), 7.02 (d,2H,H-C5,$\underline{J}_{orto}$=9.00Hz), 7.35 (d, 2H,H-C6,$\underline{J}_{orto}$=9.00Hz), 7.43 ($\underline{A}$BMX-system,2H,H-C8,$\underline{J}_{AB}$=7.30,$\underline{J}_{AM}$=8.08,$\underline{J}_{AX}$=1.79Hz), 7.44 (A$\underline{B}$MX-system,2H,H-C9,$\underline{J}_{AB}$=7.30,$\underline{J}_{BM}$=1.72,$\underline{J}_{BX}$=8.31Hz), 7.73 (AB$\underline{M}$X-system,2H,H-C7,$\underline{J}_{AM}$= 8.08,$\underline{J}_{BM}$=1,72,$\underline{J}_{MX}$=0.13Hz), 8.17 (ABM$\underline{X}$-system,2H,H-C10,$\underline{J}_{AX}$=1.79,$\underline{J}_{BX}$=8.31,$\underline{J}_{MX}$=0.13Hz), ^{13}C-nmr spectra (25.2 MHz, $CDCl_3$); (off resonance): 49.9(R-CH_2-N,t), 50.5 (4,t), 83.0 (2,t), 113.4 (4a,s), 119.7 (6,d), 121.0 (10,d), 124.6 (10a,s), 125.1 (5 and 9, d), 125.7 (8,d), 127.4 (7,d), 133.1 (6a,s), 149.0 (10b,s).

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