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SYNTHESIS OF NEW BENZO[e]DIBENZOFURO[2,3-b]-OXEPIN-5(14H)-ONES.

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ABSTRACT

The new ring systems, benzo[e]dibenzofuro[2,3-b]oxepin-5(14H)-one and benzo[e]dibenzofuro[2,1-b]oxepin-5(14H)-one were obtained by cyclizing of 2-(2'-dibenzofuryloxymethyl)benzoic acid in the presence of polyphosphoric acid ester.By cyclization of the 2-(1'-methoxy-2'-dibenzofuryloxymethyl) benzoic acid was obtained benzo[e]dibenzofuro[2,3-b]-oxepin-12-methoxy-5-one with a indubitable structure. The structure of the new compounds was proved by means of ^{1}H-and ^{13}C-NMR spectra.

RESUMO

Os novos sistemas cíclcos benzo(e)dibenzofuro(2,3-b)oxepin-5(14H)-ona e benzo(e)dibenzofuro(2,1-b)oxepin-5(14H)-ona foram obtidos através de ciclização do ácido dibenzofuriloximetilbenzóico na presença do éster do ácido polifosfórico. O composto benzo(e)dibenzofuro(2,3-b)-oxepin-12-metoxi-5-ona foi obtido com estrutura inequivocável através da ciclização do ácido 2-(1'-metoxi-2'-dibenzofuriloximetil)benzóico. A estrutura dos novos compostos foi comprovada com espectros de RMN de ^{1}H e ^{13}C.

KEYWORDS : Polycyclic heterocycles/Benzodibenzofuro-oxepinones

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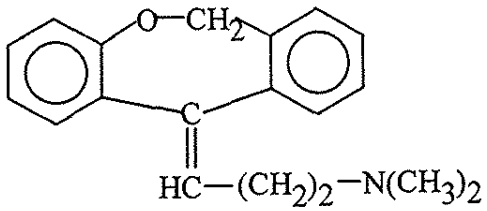
INTRODUCTION

Doxepin **(1)**, a well-known antidepressant agent[1] can be prepared by reacting the corresponding oxepinone with 3-(N,N-dimethylamino)propylmagnesium chloride[2] or with phosphorane ylides[3].



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As an important aspect of the structure-activity studies, we were interested in preparing new benzodibenzofurano-oxepinones with a view to their reaction with a Grignard compound or phosphorane ylide.

This paper reports syntheses of these new ring systems and their UV, IR, ^{1}H, ^{13}C - NMR spectra.

EXPERIMENTAL

Melting points (uncorrected) were recorded on a Büchi apparatus.The UV spectra (methanol) were recorded on a Hewlett Packard-8452A spectrophotometer.The IR spectra were obtained on a Bruker IFS-25 apparatus in KBr pellet. The NMR spectra were taken on a Bruker AM spectrometer (400 MHz and 100.6 MHz for ^{1}H and ^{13}C NMR , respectively). The spectra were recorded in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard.

2-(2'-Dibenzofuryloxymethyl) benzoic acid (4).

An amount of 10.0 g (0.054 mol) 2-hydroxydibenzofuran was added to a solution of 0.056 mole of sodium methoxide in 40 ml of dry methanol. The solvent was removed in vacuo and the resultant light brown powder **(2)** was treated with 7.60 g (0.056 mol) phthalide **(3)**. The mixture was stirred at 150 - 160^{0}C for two hours, cooled and treated with warm water. The clear solution was acidified with 4N HCl and the precipitate was removed by filtration,washed with water and dried. The crude product (13.5 g) was recrystallized from ethanol 80% to give colourless crystals, 10.5 g (60% yield) of product **4**, with m.p. 178-179^{0}C. IR (KBr): 1692 (carboxyl, C = O), 3100-2560 (carboxyl, OH) cm^{-1}. UV (methanol): λ_{max} (lg e) : 208 (4.46), 252 (4.15), 290 (4.23), 310 (3.72), 332 (3.71) nm. ^{1}H-NMR (DMSO-d_6): 8.14 (d, 1 H, H-9', J = 7.5 Hz), 7.95 (d, 1 H, H-6, J = 7.7 Hz), 7.80 (s, 1 H, H-1'), 7.33-7.78 (m, 7 H, aromatic H), 7.17 (d, 1 H, H-3', J = 8.8 Hz), 5.7 (s, 2 H, CH_2) ppm. Anal.Calcd for $C_{20}H_{14}O_4$ (318.3): C, 75.46, H 4.43; found C, 75.29, H,4.35.

Benzo(e)dibenzofuro[2,3-b]oxepin-5(14H)-one **(5a)** and benzo(e)dibenzofuro-[2,1-b] oxepin-5(14H)-one **(5b)**

A mixture of 6 g (0.042 mol) phosphorpentoxide, 12 ml dry chloroform and 8 ml dry diethyl ether was refluxed under stirring and in dry atmosphere until the mixture became clear. A quantity of 1.5 g (0.04 mol) of the compound **4** was added to this clear solution of polyphosphoric acid esther and was refluxed for two hours. The mixture was poured into ice,then extracted with chloroform.The organic layer was washed with water, 2N NaOH, water and then dried over Na_2SO_4. The chloroform was evaporated in vacuo and the crude material (1.2 g, 95% yield) was chromatographied on silicagel column. The elution of the column was realised with petrol ether (30 - 50 ^{0}C)/diethyl ether, 10/1. The first to get is **5b**. The isomere **5b** was recrystallized from diethyl ether (30% yield) and **5a** from acetic acid (50% yield). R_f value determined by TLC are 0.70 for **5a** and o.82 for **5b**.

Compound **5a:** orange crystals, m.p. 185-186^{0}C. IR (KBr): 3064, 2950 (CH), 1646 (C = O), 1232, 1025 (COC), 894, 878, 850, 828 and 807 (CH) cm^{-1}.UV (methanol): λ_{max}(lg e) = 216 (4.46), 274 (3.88), 324 (4.30) nm. ^{1}H-NMR ($CDCl_3$): 8.46 (s, 1 H, H-6), 8.05 (d, 1 H, H-11, J = 7.6 Hz), 7.95 (d, 1 H, H-4, J = 7.6 Hz), 7.59 (s, 1 H, H-12), 7.51-7.59 (m, 4 H, aromatic H), 7.35-7.46 (m, 2 H, aromatic H), 5.25 (s, 2 H, CH_2) ppm. ^{13}C-NMR ($CDCl_3$): 189.93 (C = O), 74.5 (CH_2) ppm.Anal.Calcd. for $C_{20}H_{12}O_3$ (300.3): C, 80.00, H, 4.03; found C, 79.80, H, 3.95.

Compound **5b:** pale-yellow crystals, m.p. 134-136 ^{0}C. IR (KBr): 3067, 2967, 2862(CH), 1652 (C = O), 1225, 1023 (COC), 900, 850, 823, 816 (CH) cm^{-1}.UV (methanol): λ_{max}(lg e): 214 (4.42), 258 (3.94), 324 (3.91) nm. ^{1}H-NMR ($CDCl_3$): 8.58 (d, 1 H, H-6, J = 8.2 Hz), 8.23 (d, 1 H, H-4, J = 7.5 Hz), 7.66 (d, 1 H, H-11, J = 8.8 Hz), 7.28 - 7.59 (m, 6 H, aromatic H), 7.22 (d, 1 H, H-12, J = 8.8 Hz), 5.35 (s, 2 H, CH_2) ppm. ^{13}C-NMR ($CDCl_3$) : 191.54 (C = O), 75.0 (CH_2) ppm.Anal.Calcd. for $C_{20}H_{12}O_3$ (300.3) : C,80.00; H,4.03.found: C,79.6 : H,3.80

1-Bromo-2-hydroxydibenzofuran **(6)**

This compound was obtained as colourless needles from 2-hydroxydibenzofuran with the bromine : dioxane complex (93% yield) and separated by fractional cristallization from ethanol-water, m.p. 126-127^{0}C (lit. 9, m.p. 122 - 123^{0}C).

1-Methoxy-2-hydroxydibenzofuran (7)

To a solution of 0.4 g (0.017 mol) of sodium in dry methanol (8 ml) was added 1 g (0.004 mol) of 6 and 0.3 g (0.002 mol) $CuCl_2 \circ 2H_2O$ in 4 ml DMF. The reaction mixture was heated at 110 - 115 ^{0}C for one hour. In this time 6.5 ml methanol was distilled. After heating for 5 min. at 130 ^{0}C, the mixture was cooled, treated with 10 ml water, acidified with 2N HCl to pH = 3 and extracted with diethyl ether. The extracte was then washed with water and dried on $MgSO_4$. The evaporation of solvent afforded 0.6 g (75% yield) of crude product, m.p. 120-122 ^{0}C. After recrystallization from diethyl ether-petrol ether, m.p. = 124 - 125 ^{0}C. IR(KBr): 3550 (OH), 2940, 2840 (aliphatic CH), 1220, 1012 (COC), 805, 771, 760 (CH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 9.40 (s, 1 H, OH), 8.10 (d, 1 H, H-9, J = 7.6 Hz), 7.65 (d, 1 H, H-6, J = 8.1 Hz), 7.51 (t, 1 H, H-7), 7.40 (t, 1 H, H-8), 7.29 (d, 1 H, H-4, J = 8.7 Hz), 7.11 (d, 1 H, H-3, J = 8.7 Hz), 4.07 (s, 3 H, CH_3),ppm. MS (70 ev); m/z (%) = 214 (92) [M^+], 199 (100), [M^+-15].Anal.Calcd.for $C_{13}H_{10}O_3$ (214.2): C, 72.89, H, 4.71; found C, 73.20, H, 4.60.

2-(1'-Methoxy-2'-dibenzofuryloxymethyl)benzoic acid (8)

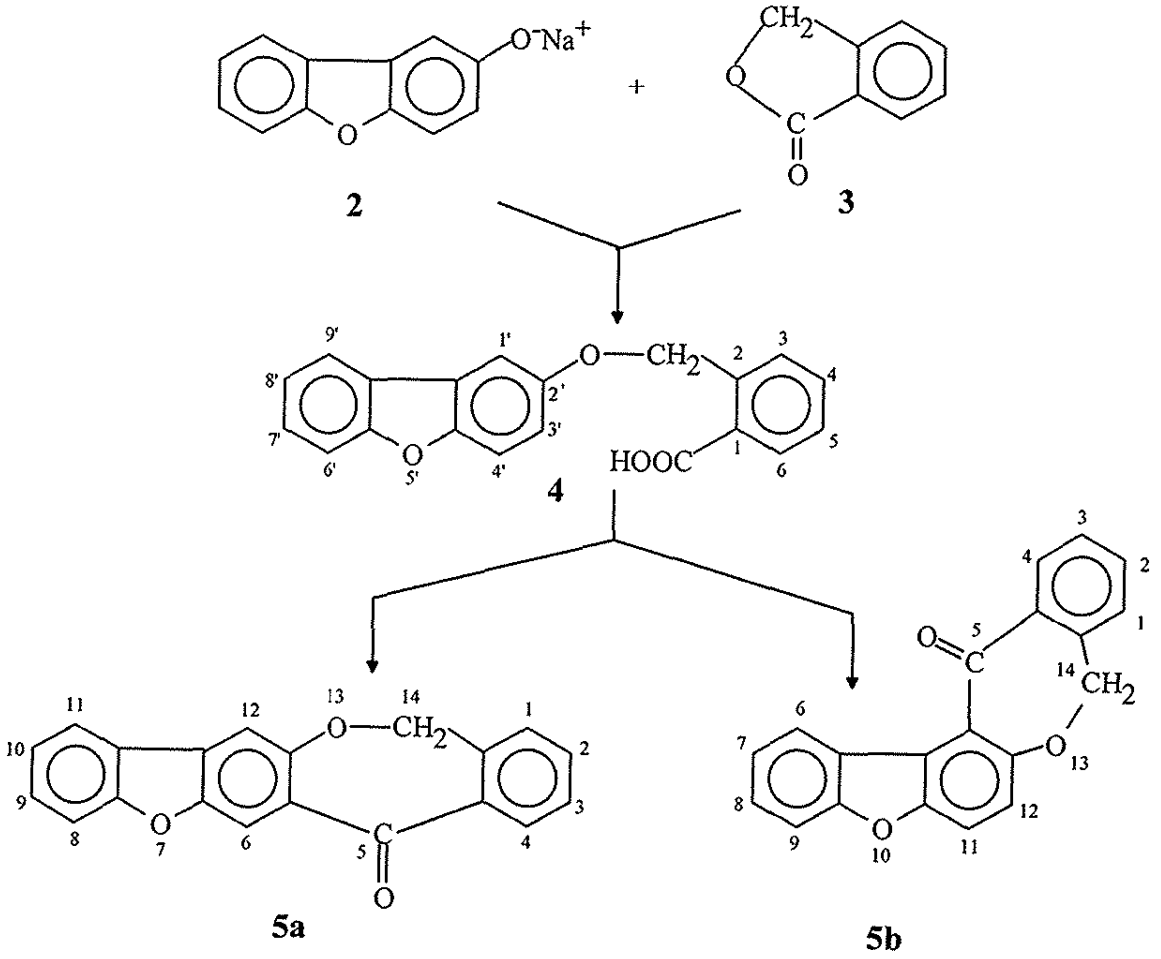
Starting from 3.2 g (0.015 mol) of 7 under the circumstances described above for **4** , but heating at 160 - 165^{0}C for 3 - 3.5 hours, we obtained 2 g (38.5%, yield) of crude product with m.p. 173 - 174^{0}C. After recrystallization from ethanol the pure **8** was obtained (colourless crystals, m.p.= 179 - 180^{0}C). ^{1}H-NMR (DMSO-d_6): 13.1 (s, 1 H, COOH), 8.10 (d, 1 H, H-9', J = 7.4 Hz), 7.98 (d, 1 H, H-6, J = 7.8 Hz), 7.80 (d, 1 H, H-6', J = 7.6 Hz), 7.40 - 7.70 (m, 5 H, aromatic H), 7.39 (d, 1 H, H-4', J = 8.8 Hz), 7.28 (d, 1 H, H-3', J = 8.8 Hz), 5.54 (s, 2 H, CH_2),ppm.^{13}C-NMR (DMSO-d_6): 168.48 (COOH), 70.42 (CH_2), 60.87 (CH_3) ppm.Anal.Calcd.for $C_{21}H_{16}O_5$ (348.4): C, 72.40, H, 4.63; found C, 72.65, H, 4.58.

12-Methoxybenzo(e)dibenzofuro[2,3-b]-oxepin-5(14H)-one (9)

Starting from 1.5 g (0.004 mol) of 8 in conditions shown by the preparation of 5, the crude product (1.3 g, 91% yield, m.p. = 165 - 175 ^{0}C) was obtained. After recrystallization from ethanol, the methoxyoxepinone 9 was obtained (m.p. = 188 - 189 ^{0}C). IR (KBr): 1645 cm^{-1} (C = O). UV (methanol):λ_{max}(lg e) : 207 (4.52), 224 (4.62), 268 (3.92), 324 (4.42) nm. ^{1}H-NMR (DMSO-d_6): 8.16 (d, 1 H, H-11, J = 7.5 Hz), 8.07 (s, 1 H, H-6), 7.96 (d, 1 H, H-4, J = 8.0 Hz), 7.27 - 7.46 (m, 6 H, aromatic H), 5.46 (s, 2 H, CH_2), 4.07 (s, 3 H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6): 188.58 (C = O), 74.20 (CH_2), 60.75 (CH_3) ppm. MS (70 ev); m/z (%): 330.4 (100) [M^+], 315.4 (20) [M^+-15]. Anal.Calcd. for $C_{21}H_{14}O_4$ (330.4): C, 76.35, H, 4.27; found C, 76.10, H, 4.35.

RESULTS AND DISCUSSION

The pathway to benzodibenzofuro-oxepinones begins with 2-hydroxy-dibenzofuran (sodium salt) (**2**). (Scheme 1).



5a **5b**

SCHEME 1

The acid **4** was prepared by the condensation of sodium salt of **2** with phthalide (**3**)[4] and the structure of the product was established through elemental analysis, IR and ^{1}H-NMR spectra. The IR spectrum of the compound **4** shows absorption bands at 1692 (carboxyl, C = O) and 3000-2560 cm^{-1} (carboxyl, OH).The ^{1}H-NMR spectrum exhibits the signal of the methylene = 5.56 ppm and also of the carboxyl group (δ = 13.1 ppm) .

The ring closure of the compound **4** was made according to Maior and Wolff[5] with polyphosphoric acid ester (prepared cf. ref. 6) in chloroform. Compounds **5a** and **5b** were obtained in almost equal percentage and were separated by column chromatography (silicagel).

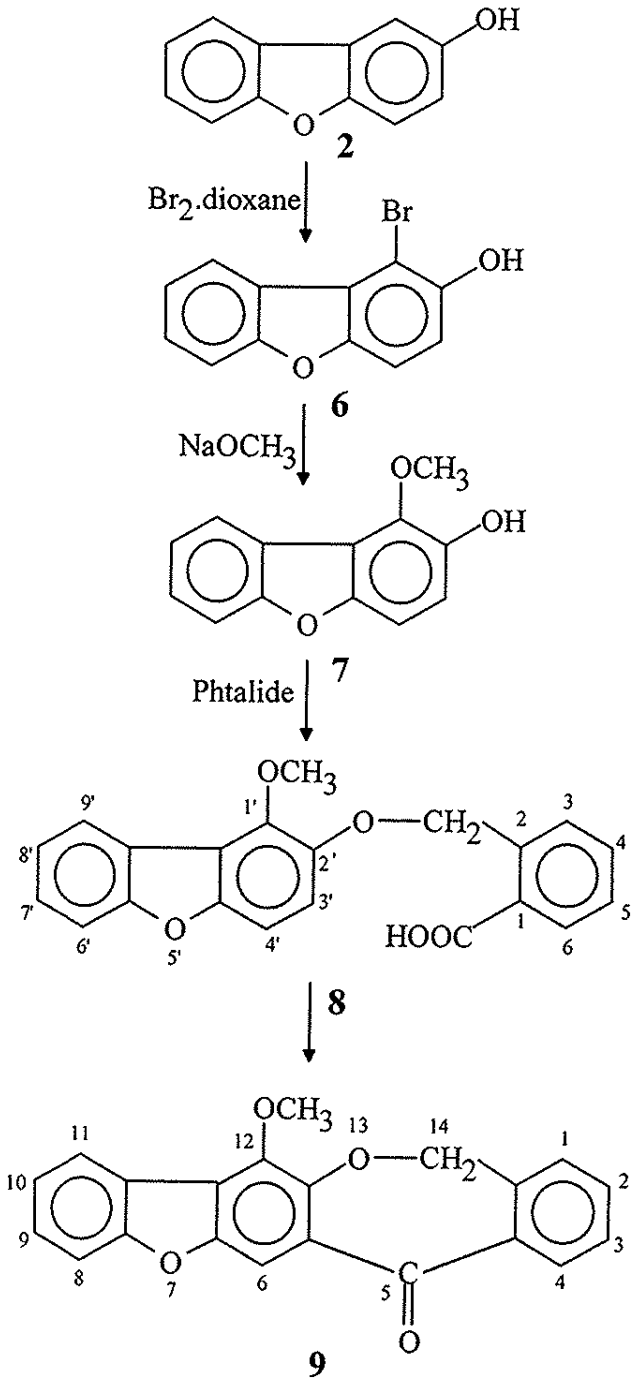
The unequivocable structure of **5a** and **5b** was established by means of ^{1}H-NMR spectrum. The inspection of the spectrum of the compound **5a** allows the assignment of the resonance singlets at d = 8.46 and 7.59 to the proton H-6, (deshielded by carbonyl group) and H-12, respectively. The doublets signals from the spectrum of the compound **5b** at d = 7.66 and 7.22 ppm were assigned to the protons H-11 and H-12, respectively. These chemical shift assignments are in agreement with the data of the parents compounds, dibenzofuran[7] and dibenzo[b,e]oxepin-11(6H)-one[8].

In order to have another benzodibenzofuro-oxepinone with linear structure, we have utilized the reactions from Scheme 2.

The compound **6**, prepared for the first time by Gilman et all[9] from **2** by reaction with bromine in acetic acid, was obtained by us more conveniently by using the Br_2-dioxane complex. The IR spectrum of **6** showed absorption bands for hydroxyl group at $\tilde{\upsilon}$ = 3540 cm^{-1} and at 750 , 810 cm^{-1} assigned to γ_{4CH} , γ_{2CH} ,respectively.

Treatment of **6** with sodium methoxide in the presence of $CuCl_2 \cdot 2H_2O$ in DMF leads to 1-methoxy-2-hydroxydibenzofuran (**7**). The IR spectrum of **7** exhibits two absorption bands located at 1226 and 1015 cm^{-1} assigned to the methoxyl group and mass spectrum shows the molecular ion at m/z = 214 and the [M^+- CH_3] peak at 199 (base peak). We have observed that due to the very strong magnetic field (400 MHz) as well as to the methoxy and hydroxyl groups, the ^{1}H-NMR spectrum of **7** exhibits 4 doublets corresponding to the protons H-3, H-4, H-6 and H-9, two triplet signals assignable to the protons H-7 and H-8 and one singlet due to the hydroxyl group (first order spectrum).

The phenoxide of **7** was then condensed whith phthalide and from mixture the acid **8** was separated. This was characterized by IR, ^{1}H-NMR and Mass spectra. The IR spectrum displays absorbtion at 1695 and 3100-2650 cm^{-1} (large band) assigned to the stretching vibrations of the carboxyl group. The band assigned to the hydroxyl group is absent. The ^{1}H-NMR spectrum of **8** shows signals corresponding to the carboxyl (δ = 13.1 ppm), aromatic protons (δ = 8.1 - 7.2 ppm), methylene (δ = 5.54 ppm) and methyl (δ = 4.07 ppm).


OH
O
2
Br2.dioxane
Br
OH
O
6
NaOCH3
OCH3
OH
O
7
Phtalide
OCH3
O—CH2
HOOC
8
OCH3
O—CH2
O
C
O
9

SCHEME 2

The ring closure of **8** has also been carried out with polyphosphoric acid ester in chloroform. Infrared spectrum of **9** shows no absorption band due to the carboxyl, but displays a band at 1650 cm^{-1} assigned to the carbonyl group. The ^{1}H-NMR spectrum exhibits multiplet corresponding to the aromatic protons and also two singlet signals assigned to the methylene (= 5.46 ppm) and methyl group (= 4.07 ppm). The mass spectrum shows the molecular ion at m/z = 330 (base peak).

Generally, linear polycyclic aromatic compounds absorb at longer wave-lengths than the corresponding angular one[10]. Except for the band at longest wave-length (λ =324 nm) the other absorption bands from the UV spectrum of the oxepinone **5b** (angular) are slightly hypsochromic shifted in comparison with the correspoding bands of the oxepinone **5a** and **9** (linear). The UV spectra of 5a and **9** are similar, but the expected bathochromic shift induced by the presence of the methoxyl group cannot be observed.

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