Monatshefte für Chemie 130, 1475–1480 (1999)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Synthesis and Structural Characterization of 6,11-Dihydrodibenz[*b,e*]oxepinones

Wolf-Dieter Rudorf[1,*], **Ute Baumeister**[2], **Stelian Florea**[3], **Anca Nicolae**[4], and **Ovidiu Maior**[4]

[1] Institute of Organic Chemistry, Martin Luther University, D-06099 Halle, Germany
[2] Institute of Physical Chemistry, Martin Luther University, D-06099 Halle, Germany
[3] Department of Chemistry, University of Craiova, RO-1100 Craiova, Romania
[4] Department of Organic Chemistry, University of Bucharest, RO-70031, Bucharest, Romania

Summary. 6,11-Dihydrodibenz[*b*,*e*]oxepin-11-ones were obtained by cyclodehydration of 2-(phenoxymethyl)-benzoic acids prepared by reaction of the corresponding phenols with phthalids. Cyclodehydration was found to be most effective using polyphosphoric acid ester. The structure of one of the title compounds was determined by X-ray crystal structure analysis.

Keywords. Cyclodehydration; 6,11-Dihydrodibenz[*b*,*e*]oxepin-1-one; 2-(Phenoxymethyl)-benzoic acid; Phthalide; X-Ray structure determination.

Synthese und strukturelle Charakterisierung von 6,11-Dihydrodibenz[*b,e*]oxepinonen

Zusammenfassung. 6,11-Dihydrodibenz[*b*,*e*]oxepin-11-one wurden durch Cyclodehydratisierung von 2-(Phenoxymethyl)-benzoesäuren – hergestellt durch Reaktion der entsprechenden Phenole mit Phthaliden – erhalten. Die Cyclodehydratisierung war am effektivsten bei Verwendung von Polyphosphorsäureester. Eine der Titelverbindungen wurde durch Röntgenstrukturanalyse charakterisiert.

Introduction

The dibenz[*b*,*e*]oxepin nucleus constitutes the fundamental structure of many products with biological activity [1–3]; the best known representative is 11-(3-dimethylaminopropylidene)-6*H*-dibenz[*b*,*e*]oxepin hydrochloride which is used as the antidepressant agent doxepin [4]. A series of 11-(4-cinnamyl-1-piperazinyl)-6,11-dihydrodibenz[*b*,*e*]oxepins is of interest for treatment of cerebrovascular disorders [5], and 6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid derivatives show potent antiallergic activities [6, 7]. In continuation of our investigations on the class of dibenz [*b*,*e*]oxepinones [8, 9] we wish to report the results of our study of the reactions of the isomeric phenols **1a** and **1b** with phthalide and 5,6-dimethoxyphthalide.

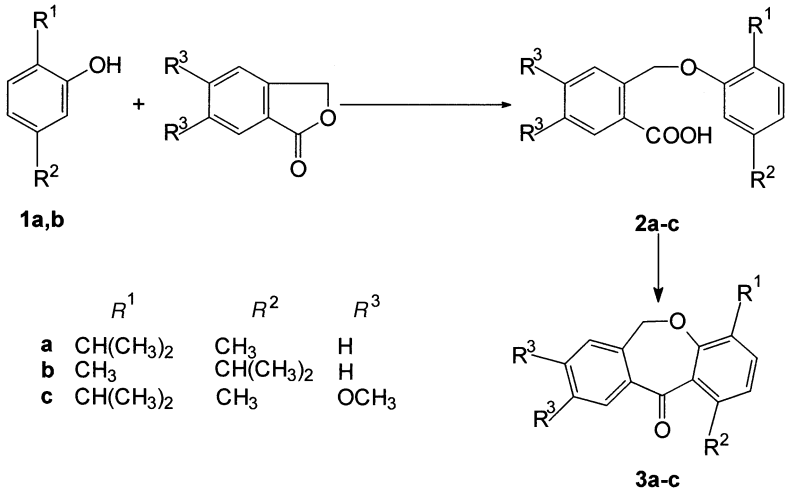
* Corresponding author

Results and Discussion

The target compounds were synthesized as outlined in Scheme 1. 6,11-Dihydrodibenz[*b*,*e*]oxepin-11-ones **3a–c** were obtained by cyclodehydration of the corresponding 2-(phenoxymethyl)-benzoic acids **2** easily prepared in acceptable yields at temperatures between 150 and 160°C using sodium methylate as base. Cyclodehydration of these carboxylic acids, which were used without further purification, was carried out in the presence of polyphosphoric ester (*PPE*). Other cyclodehydration conditions were examined but proved to be less efficient. Thus, employing trifluoroacetic anhydride and a catalytic amount of boron trifluoride diethyl etherate resulted in a yield of only 15% of **3b**. Treating 2-(phenoxymethyl)-benzoic acids **2** with polyphosphoric acid (*PPA*), however, always afforded a complex mixture, probably owing to the lability of **2** under the acidic conditions.

An attempt to introduce the N,N-dimethylaminopropylidene group in position 11 of **3a** by *Wittig* reaction with 3-(N,N-dimethylamino)-propyl triphenylphosphonium bromide hydrobromide and *n*-butyl lithium in *THF* was unsuccessful. The structure of 4-isopropyl-1-methyl-6,11-dihydrodibenz[*b*,*e*]oxepin-11-one (**3a**) was confirmed by X-ray crystal structure analysis. **3a** crystallizes in space group $P\bar{1}$ with four molecules per unit cell, but the two crystallographically independent molecules *I* and *II* are nearly identical. Therefore, only molecule *I* is shown in Fig. 1.

Bond lengths and angles in **3a** agree very well with the corresponding values found for the three-ring skeleton of 6,11-dihydro-11-oxo-dibenz[*b*,*e*]oxepin-2-acetic acid (reference compound **R1**) and its methyl and ethyl esters (**R2**, **R3**) [10]. The overall shape of the molecular core also closely resembles that of **R1**–**R3** and, additionally, that of the related 11-substituted compounds (*Z*)-11-(3-(dimethylamino)-propylidene)-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid (**R4**) [11] and methyl (11*R*)-11-(2-(4-benzylpiperidino)-ethylthio)-6,11-dihydrobenz[*b*,*e*]oxepin-2-carboxylate (**R5**) [12]. The interplanar angle between the two phenyl rings describing the folding of the tricyclic skeleton amounts to 41 and 42° for molecule



	R^1	R^2	R^3
a	$CH(CH_3)_2$	CH_3	H
b	CH_3	$CH(CH_3)_2$	H
c	$CH(CH_3)_2$	CH_3	OCH_3

Scheme 1

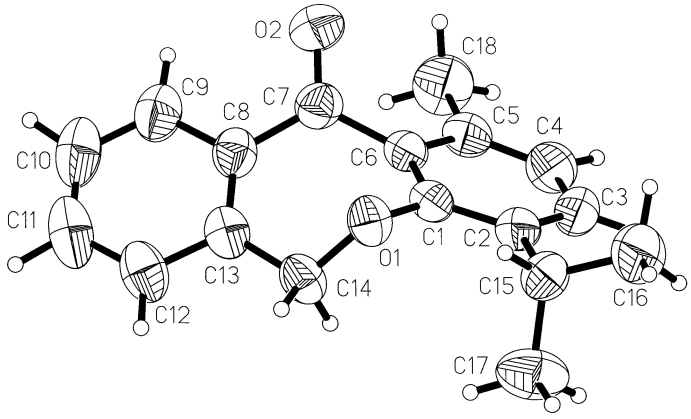


Fig. 1. Molecular structure of molecule *I* of **3a** (displacement ellipsoids on the 50% probability level)

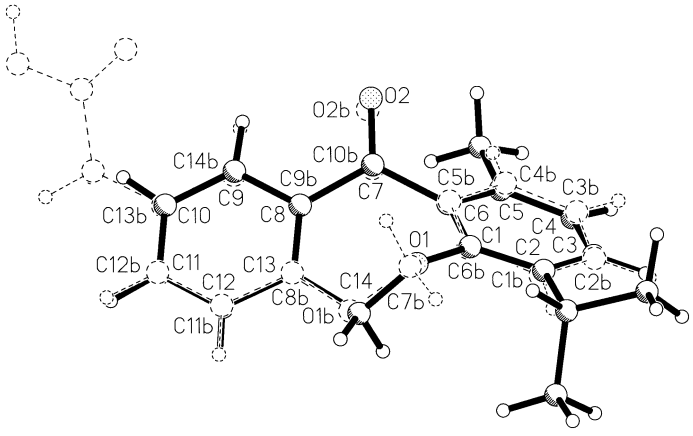


Fig. 2. Superposition of the molecular structures of molecule *I* of **3a** (full lines) and 6,11-dihydro-11-oxo-dibenz[*b*,*e*]oxepin-2-acetic acid (**R1**, dashed lines and atoms labeled with *b* [10])

I and *II*, respectively; the same angles range from 49.0 to 31.5° for the five reference compounds. The distances between the centres of the two phenyl rings are 5.174 and 5.164 Å and fit well in the range of corresponding values of **R1** and **R5** and other biologically active compounds containing similar tricyclic skeletons [13]. The same holds for the twist of the two phenyl rings with respect to one another which is fixed by the conformation of the central seven-membered ring and may be quantified by the angle between the lines through C1 and C6 on the one hand and C8 and C13 on the other hand (33.4(2) and 32.4(2)° for molecules *I* and *II*, respectively).

The conformation of the dihydrooxepin ring of **3a** differs from that in **R1** to **R5**: both O atoms of **3a** lie on the same side of the least-squares plane through the seven ring atoms, whereas in the reference molecules thy lie on opposite sides. However, an inspection of the corresponding torsion angles (cf. Table 1) reveals in principle the same conformation as found for **R1** to **R5** when the molecule is turned around an axis through C7 and the midpoint of the C14−O1 bond in a way

Table 1. Endocyclic torsion angles (*E*) for the seven-membered ring of **3a**

Atoms	Torsion angle/°	
	Molecule *I*	Molecule *II*
C6–C7–C8–C13	21.0(3)	19.5(3)
C7–C8–C13–C14	5.8(4)	8.0(4)
C8–C13–C14–O1	29.4(3)	27.9(3)
C13–C14–O1–C1	−86.7(2)	−88.5(2)
C14–O1–C1–C6	67.7(2)	72.1(2)
O1–C1–C6–C7	11.0(3)	7.4(3)
C1–C6–C7–C8	−53.0(3)	−50.6(3)

that the two phenyl rings adopt exchanged positions with respect to the reference compounds. Hence, C14 corresponds to the ring O atom of **R1** to **R5** and O1 to the neighbouring C atom as shown in Fig. 2 by a superposition of the molecular structures of **3a** and **R1**.

Experimental

^{1}H NMR: Gemini 2000 (400 MHz); ^{13}C NMR: Gemini 2000 (100 MHz); IR: Perkin-Elmer FT-IR Spectrometer SPECTRUM 1000; melting points: Boetius melting point apparatus; EI-MS: AMD Intectra GmbH AMD 402; TLC: Merck silica gel 60 F_{254}, petroleum ether 35–65°C/toluene/acetone/methanol (10:7:2:1); elemental analysis: Leco CHNS-932. The elemental analyses agreed satisfactorily with the calculated values. 5,6-Dimethoxyphthalide was prepared from 3,4-dimethoxybenzoic acid according to Refs. [14, 15].

2-Phenoxymethyl-benzoic acids (**2**; *general procedure*)

Thymol or carvacrol (20 mmol) were added to a solution of 0.46 g (20 mgatom) Na in 12 cm^3 dry methanol. The solvent was removed *in vacuo* and the solid was treated with 25 mmol phthalide or 5,6-dimethoxyphthalide. The mixture was stirred at 150–160° for 4 h, cooled, and treated with 50 cm^3 warm H_2O. The clear solution was acidified with 4 *N* HCl and the precipitate was removed by filtration, washed with water and dried.

2-(2′-Isopropyl-5′-methyl-phenoxymethyl)-benzoic acid (**2a**; $C_{18}H_{20}O_3$)

Yield: 5.2 g (92%); m.p.: 162–163°C (ethanol); TLC: $R_f = 0.52$; IR (KBr): $\tilde{\nu} = 3000$–2500, 1687 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.14 (d, 6H, $J = 7$ Hz), 2.23 (s, 3H), 3.27 (m, 1H), 5.40 (s, 2H), 6.6–6.8 (m, 2H), 7.07 (d, 1H, $J = 7.6$ Hz), 7.44 (t, 1H, $J = 7.7$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 7.69 (d, 1H, $J = 7.5$ Hz), 7.94 (dd, 1H, $J = 7.7$ and 1.2 Hz), 13.00 (s, 1H) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 67.8 (O–CH_2), 168.3 (COOH) ppm; MS (EI, 70 eV): $m/z = 284$ (M^+).

2-(5′-Isopropyl-2′-methyl-phenoxymethyl)-benzoic acid (**2b**; $C_{18}H_{20}O_3$)

Yield: 5.35 g (94%); m.p.: 144–145°C (ethanol); TLC: $R_f = 0.57$; IR (KBr): $\bar{\nu}$ =3200–2500, 1682 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.14 (d, 6H, $J = 6.6$ Hz), 2.16 (s, 3H), 2.79 (m, 1H),

5.42 (s, 2H), 6.70 (dd, 1H, $J = 7.8$ and 1.3 Hz), 6.78 (d, 1H, $J = 1.3$ Hz); 7.03 (d, 1H, $J = 7.62$ Hz), 7.42 (td, 1H, $J = 7.8$ and 0.8 Hz), 7.59 (td, 1H, $J = 7.6$ and 1.3 Hz), 7.69 (d, 1H, $J = 7.6$ Hz), 7.91 (dd, 1H, $J = 7.8$ and 1.3 Hz), 13.03 (s, 1H) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 67.5 (O–CH_2), 168.5 (COOH) ppm; MS (EI, 70 eV): $m/z = 284$ M^+).

4,5-Dimethoxy-2(2′-isopropyl-5′-methyl-phenoxymethyl)-benzoic acid (**2c**; $C_{20}H_{24}O_5$)

Yield: 4.48 g (65%); m.p.: 169–171°C (ethanol); TLC: $R_f = 0.50$; IR (KBr): $\bar{\nu}$ =3200–2500, 1682 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz): 1.16 (d, 6H, $J = 6.8$ Hz), 2.24 (s, 3H), 3.26 (m, 1H), 3.8 (s, 6H), 5.36 (s, 2H), 6.70 (d, 1H, $J = 7.8$ Hz), 6.76 (s, 1H), 7.05 (d, 1H, $J = 7.8$ Hz), 7.30 (s, 1H), 7.49 (s, 1H), 12.80 (s, 1H) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 67.4 (O–CH_2), 167.7 (COOH) ppm.

6,11-Dihydrodibenz[b,e]oxepin-11-ones (**3**; *general procedure*)

A mixture of 6 g (42 mmol) phosphorus pentoxide, 12 cm^3 anhydrous chloroform, and 6 cm^3 anhydrous diethyl ether was refluxed until the mixture became clear. The corresponding 2-phenoxymethyl-benzoic acid **2** (8 mmol) was added to this solution of polyphosphoric ester (*PPE*) and refluxed for 1 h. The cold mixture was poured into 150 cm^3 ice water and extracted with chloroform (twice, 100 cm^3 each). The combined organic phases were successively washed with water and 2 *N* NaOH and then dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure at 40°C. The residue was purified by recrystallization or column chromatography on silica gel (petroleum ether/toluene/acetone/methanol = 10:7:2:1).

4-Isopropyl-1-methyl-6,11-dihydrodibenz[b,e]oxepin-11-one (**3a**; $C_{18}H_{18}O_2$)

Yield: 2 g (93%); m.p.: 80–81°C (ethanol); TLC: $R_f = 0.87$; IR (KBr): $\bar{\nu}$ =1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.26 (d, 6H, $J = 6.8$ Hz), 2.38 (s, 3H), 3.38 (m, 1H),5.25 (s, 2H), 7.00 (d, 1H, $J = 7.8$ Hz), 7.15 (d, 1H, $J = 7.6$ Hz), 7.25 (d, 1H, $J = 7.8$ Hz), 7.42 (t, 1H, $J = 7.5$ Hz), 7.49 (td, 1H, $J = 7.6$ and 1.4 Hz), 8.02 (dd, 1H, $J = 7.6$ and 1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 75.5 (O–CH_2), 197.0 (C=O) ppm; MS (EI, 70 eV): $m/z = 266$ (M^+).

I-Isopropyl-4-methyl-6,11-dihydrobenz[b,e]oxepin-11-one (**3b**; $C_{18}H_{18}O_2$)

Yield: 1.1 g (53%); oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.18 (d, 6H, $J = 6.8$ Hz), 2.30 (s, 3H), 3.22 (m, 1H), 5.24 (s, 2H), 7.07 (d, 1H, $J = 8.0$ Hz), 7.09 (d, 1H, $J = 7.2$ Hz), 7.22 (d, 1H, $J = 8.0$ Hz), 7.37 (t, 1H, $J = 7.2$ Hz), 7.45 (td, 1H, $J = 7.6$ and 1.4 Hz), 7.91 (dd, 1H, $J = 7.8$ and 1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 73.5 (O–CH_2), 197.4 (C=O) ppm.

4-Isopropyl-1-methyl-8,9-dimethoxy-6,11-dihydrodibenz[b,e]oxepin-11-one (**3c**; $C_{20}H_{22}O_4$)

Yield: 1.1 g (42%); m.p.: 152–153°C (diethyl ether); TLC: $R_f = 0.68$; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.25 (d, 6H, $J = 7.0$ Hz), 2.39 (s, 3H), 3.36 (m, 1H), 5.17 (s, 2H), 6.60 (s, 1H), 7.00 (d, 1H, $J = 7.9$ Hz), 7.23 (d, 1H, $J = 7.9$ Hz), 7.66 (s, 1H) ppm; MS (EI, 70 eV): $m/z = 326$ (M^+) .

X-Ray crystal structure analysis of **3a**

$C_{18}H_{18}O_2$, $M_w = 266.32$, triclinic, space group $P\bar{1}$, $a = 8.069(1)$, $b = 13.494(3)$, $c = 13.903(2)$ Å, $\alpha = 78.89(1)$, $\beta = 76.74(1)$, $\gamma = 85.70(1)°$, $V = 1445.2(4)$ $Å^3$, $Z = 4$, $F(000) = 568$. Data were

measured on a Stoe STADI4 diffractometer using graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods of phase determination and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for non-H atoms. Hydrogen atom positions were derived from a difference *Fourier* map and refined with isotropic displacement parameters. Final *R*-values are $wR_2 = 0.1454$ (8408 unique reflections, 506 refined parameters) and $R_1 = 0.0695$ (3963 observed reflections with $I \geq 2\sigma(I)$). Calculations and drawings were performed using the programs SHELXS-97 [16], SHELXL-97 [17], and Siemens XP/PC [18]. Additional material to the structure determination may be ordered from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, referring to the deposition number CCDC 127522, the names of the authors, and the citation of the present paper.

Acknowledgements

S. F. would like to thank the *DAAD* for financial support.

References

[1] Obshima E, Kana F, Sato H, Obase H, Kumazawa T, Takahara S, Ohno T, Ishikawa T, Yamada K (1993) Eur Pat Appl EP 549352; (1993) Chem Abstr **119**: 249955
[2] Allen RC, Helsley GC, Hamer RRL, Freed BS, White JI, Martin LL Can Pat Appl 2023951; (1991) Chem Abstr **115**: 114378
[3] Kumazawa T, Yanase M, Harakawa H, Obase H, Skirakura S, Ohishi E, Oda S, Kubo K, Yamada K (1994) J Med Chem **37**: 804
[4] Dictionary of Pharamacological Agents vol 1 (1997) Chapman & Hall, London Weinheim New York Tokyo Melbourne Madras, p 765
[5] Kurokawa M, Sato F, Masuda Y, Yoshida T, Ochi Y, Zushi K, Fujiwara I, Naruto S, Uno H, Matsumoto J (1991) Chem Pharm Bull **39**: 2564
[6] Kamazawa T, Ohshima E, Harakawa H, Sato H, Obase H, Oiji Y, Ishii A, Ishii H, Ohmori K (1991) Chem Pharm Bull **39**: 2729
[7] Ohshima E, Kumazawa T, Takizawa H, Harakawa H, Sato H, Obase H, Oiji Y, Ishii A, Ishii H, Ohmori K (1991) Chem Pharm Bull **39**: 2724
[8] Maior OC, Wolff AD, Rom Pat 62927; (1980) Chem Abstr **92**: 163855
[9] Florea S, Nicolae A, Maior O (1996) South Braz J Chem **4**: 101; (1997) Chem Abstr **127**: 234269
[10] Matsuzawa ES, Hirayama N, Ohshima E, Obase H (1992) Acta Crystallogr **C48**: 2016
[11] Ohshima E, Otaki S, Sato H, Kumazawa T, Obase H, Ishii A, Ohmori K, Hirayama N (1992) J Med Chem **35**: 2074
[12] Hirayama N, Sugaya T, Tomioka S, Ohshima E, Obase H (1993) Acta Crystallogr **C49**: 600
[13] Reboul JP, Soyfer JC, Cristau B, Darbon N, Oddon Y, Pepe G (1983) Acta Crystallogr **C39**: 600
[14] Ray JN, Robinson R (1925) J Chem Soc **127**: 1618
[15] Leblois D, Piessard S, Le Baut G, Kumar P, Brion JD, Sparfel L, Sanchez RY, Juge M, Petit JY, Welin L (1987) Eur J Med Chem Chim **22**: 229
[16] Sheldrick GM (1990) Acta Crystallogr **A46**: 467
[17] Sheldrick GM (1997) SHELXL-97: Program for the refinement of crystal structures. University of Göttingen, Germany
[18] XP/PC, Molecular graphics program package for display and analysis of stereochemical data, V. 4.2 for MS-DOS (1990) Siemens Analytica X-ray Instruments, Inc., Madison, Wisconsin, USA

Received May 31, 1999. Accepted June 21, 1999