Arch. Pharm. (Weinheim) *319*, 457–461 (1986)

Stereospecificity of the Photoinduced Conversion of Methylphenobarbital to Mephenytoin

Henryk J. Bartoń, Jacek Bojarski* and Aleksandra Żurowska

Department of Organic Chemistry, Nicolaus Copernicus Academy of Medicine, Dzierżyńskiego 14 B st., 30–048 Kraków, Poland

Eingegangen am 23. April 1985

Photochemically, an anion of *S*(+)-5-ethyl-1-methyl-5-phenylbarbituric acid is converted stereospecifically to *R*(–)-5-ethyl-3-methyl-5-phenylhydantoin at room temperature. The *R* configuration is proposed for (–)-5-allyl-3-methyl-5-phenylhydantoin.

Stereospezifizität der photoinduzierten Umwandlung von Methylphenobarbital zu Mephenytoin

Ein Anion der *S*(+)-5-Ethyl-1-methyl-5-phenylbarbitursäure wird bei Raumtemperatur photochemisch und stereospezifisch in *R*(–)-5-Ethyl-3-methyl-5-phenylhydantoin umgewandelt. Für (–)-5-Allyl-3-methyl-5-phenylhydantoin wird *R* Konfiguration vorgeschlagen.

In our earlier investigation on photolysis of methylphenobarbital[1] **(1a)** it was found that the barbituric acid ring undergoes contraction yielding 5-ethyl-3-methyl-5-phenylhydantoin **(2a)**. This conversion took place in an alkaline medium where **1a** is ionized and was accompanied by the evolution of CO. Similar contraction was found also for the photolysis of N-methylbarbital but in this case the product of ring opening – N-(2-ethylbutyryl)-N-methylurea – was also isolated[2].

Since methylphenobarbital is a chiral compound and its enantiomers were separated and their configuration established[3,4,5], we decided to investigate the stereochemical course of the above mentioned photochemical reaction leading to the chiral hydantoin derivative with the absolute configuration also recently defined[6].

Preparative photolysis of *S*(+)-methylphenobarbital **(1a)** in the alkaline ethanol-water medium at ca. 15°C yielded the appropriate hydantoin derivative which showed the optical activity characteristic for *R*-mephenytoin **(2a)**: $[\alpha]_D^{20} = -101.6°$, lit.[6] –105.6°. The optical purity of the isolated mephenytoin was checked by the HPLC method according to *Sybilska* et al.[7] using β-cyclodextrin as a chiral component of the mobile phase and an RP-18 column. It was found that the hydantoin obtained does not contain enantiomeric *S*(+)-mephenytoin and that the remaining substrate does not change its steric structure (Fig. 1).

Chromatographic results also indicated that *R*(–)-**1a** was photolysed yielding *S*(+)-**2a**. Similar experiments for *S*(+)- and *R*(–)-5-allyl-1-methyl-5-phenylbarbituric acids **(1b)** revealed that both enantiomers are photolysed at room temperature to appropriate, enantiomeric hydantoins. Preparative photolysis of *S*(+)**1b** yielded 5-allyl-3-methyl-

0365–6233/86/0505–0457 $ 02.50/0

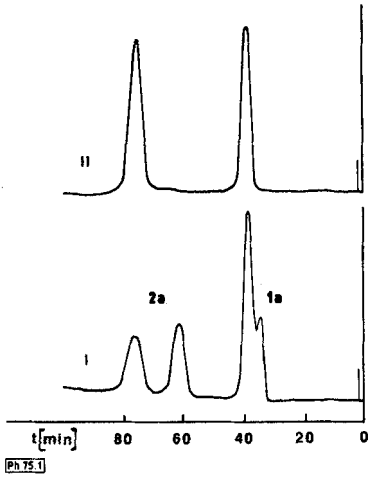


Fig. 1: HPLC separations: I: mixture of racem. **1a** and **2a** with addition of *S*(+)**1a**, II: photolysate of *S*(+)**1a**.

5-phenylhydantoin **(2b)** with $[\alpha]_D^{20}$ EtOH = −102.6°. The structure of this compound was fully confirmed by the MS and ^{1}H-NMR spectra.

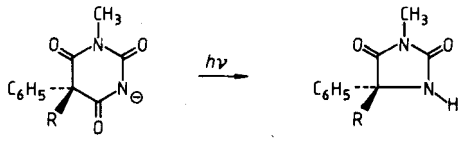
The investigated barbiturate substrates with the same configuration show very similar retention times, order of elution and specific rotation values. The same is true for the hydantoin products (Tab. 1), and in both cases the reaction is stereospecific.

Table 1: *Comparison of HPLC retention times and optical rotations of investigated compounds*

Compd.	*R*(−)		*S*(+)		α^b
	t_r (min)	$[\alpha]_D^{20}$	t_r (min)	$[\alpha]_D^{20}$	
1a	34.1	−8.7[a]	38.0	+8.9[a]	1.12
1b	35.3	−5.0[a]	38.8	+5.6[a]	1.11
2a	75.4 (*S*)[c]	−105.6[d]	61.1 (*R*)	+106.0[d]	1.24
2b	73.6 (*S*)	−102.6	59.9 (*R*)		1.24

a: lit.[8], for **1a** −8.5 and +8.2° from lit.[4]; b: selectivity of resolution of enantiomers in HPLC; c: configuration of barbiturate substrates are given in parentheses; d: lit.[6].

Since methylphenobarbital yields mephenytoin with the same arrangement of substituents at the C-5 atom (only the sign of configuration is changed, for instance from the substrate of *S* configuration the *R* hydantion is formed) one can assume that from *S*-5-allyl-1-methyl-5-phenylbarbituric acid the appropriate hydantoin formed has also the configuration of C-5 substituents retained i.e. it has the *R* configuration.

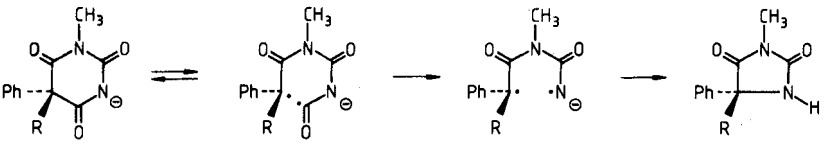


1 **2**

Scheme 1: **a**: *S*(+) R = CH_3CH_2 **a**: *R*(−)
b: *S*(+) R = CH_2=$CHCH_2$ **b**: *R*(−)

We investigated also the photolysis of S(+)**1a** at elevated temperatures. At 40°C no significant differences were found in the steric course of the reaction compared with that at room temperature, at 80°C however, the presence of ca. 20 % of *S*(+) enantiomer of mephenytoin was found along with ca. 80 % of *R*(−)**2a** with the retained configuration. Moreover a partial racemization of the remaining substrate was also observed.

We suggested earlier[1] that the conversion of **1a** to **2a** occurs through the intermediate biradical formed by the homolytic fission of the C-4 – C-5 or N-3 – C-4 bonds of the pyrimidine ring. The partial racemization of the substrate mentioned above seems to eliminate this second possibility, if one assumes that this relatively small increase of the temperature (40°C) does not cause the qualitative change in the reation mechanism. It also proves that the process of the ring opening is reversible, as it frequently takes place in the photochemical behavior of other cyclic carbonyl systems, where the radical mechanism of α-cleavage occurs[8].



1 **2**

Scheme 2: R = CH_3CH_2, CH_2 = $CHCH_2$

The earlier[1] reported relatively low quantum yield of photolysis of **1a** (φ = 0.01) is consistent with this conclusion.

We think that the stereospecific photolytic conversion of barbituric acid derivatives to corresponding hydantoins may be a convenient method of correlation of their respective absolute configurations. Further investigations of the scope of such a method are in progress.

The Authors thank Professor *J. Knabe* (University of the Saarland) for donation of samples of barbiturate enantiomers and Dr. *H. Duddeck* (Ruhr University) for MS and NMR spectra.

Experimental Part

Uncorr. m.p.'s: Boëtius apparatus (VEB Analytik, Dresden); *HPLC:* Chromatograph Liquochrom OE 307 (Labor MIM, Budapest); *UV irradiation:* low pressure mercury lamps TUV 30 (Philips) and NK 6/20 (Hanau); *optical rotation:* Hilger micropolarimeter (cuvette 1 ml, l = 0.5 dm); *^{1}H-NMR:* Bruker WP-80; *MS* (70 eV): Varian CH-5; *β-cyclodextrin* (Chinoin, Budapest).

Preparative photolysis:

0.2 g of *S*(+)**1a** or **1b** was dissolved in 10 ml of hot 96 % ethanol and diluted with 25 ml of carbonate buffer pH 9.96 (0.25 M-$NaHCO_3$, 0.14 M-NaOH) and 200 ml of distilled water. The solution was placed in cyclindrical glass reactor (vol. 0.245 l), purged with argon and equilibrated at 15°C. After irradiation (TUV 30 lamp, 2 h) the solution was evaporated to a few ml and extracted 3 times with 50 ml $CHCl_3$. The combined extracts were dried (Na_2SO_4) and the solvent was evaporated i.vac.. The residue was dissolved in 10 ml of CCl_4 and extracted twice with 10 ml portions of carbonate buffer. Combined buffer extracts were extracted with 10 ml of CCl_4 and combined CCl_4 layers washed with 2 ml of 2 M-NaOH, then with water and dried with Na_2SO_4. 5 ml of hexane was added and the solution was filtered. 15 ml of hexane was added to the filtrate which was heated until the suspension was dissolved and set aside for crystallization **(2a)**. The filtrate after crystallization was evaporated and the residue was crystallized from water yielding an additional amount of crystals **2a** and **2b.** Combined buffer layers were acidified with conc. HCl to pH~1 and extracted three times with 10 ml portions of CCl_4. From the combined organic layers the unchanged substrate was recovered: **1a** – 41 mg, **1b** – 51 mg.

The course of extractions and the purity of the product was checked by HPLC: column Ø 4.6/100 mm, RP–18 10μm; mobile phase: 50 % MeOH in H_2O, 1 mM–Na_2HPO_4; flow rate 1.44 ml/min; UV detector λ = 210 nm; retention times: barbiturates **1a, 1b** = 0.70 min, hydantoins **2a, 2b** = 1.8 min.

R(–)-*5-ethyl-3-methyl-5-phenylhydantoin* **(2a)**, 28 mg (from CCl_4 + hexane), m.p. 135–137°C and 18 mg (H_2O), m.p. 137–138°C, lit.[6] 135°C; racemic sample crystallized from CCl_4 + hexane has m.p. 137.5–138.5°C $[\alpha]_D^{20}$ (96 % EtOH, c = 0.127 M) = –101.6°, $[\alpha]_{546}^{20}$ = –126.8°, lit.[6] $[\alpha]_D^{20}$ = –105.6°.

R(–)-*5-allyl-3-methyl-5-phenylhydantoin* **(2b)**, 48 mg, m.p. 142-145°C (H_2O), $[\alpha]_D^{20}$ (EtOH absol., c = 0.154 M) = –102.6°, $[\alpha]_{556}^{20}$ = –125.7°. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.7–7.2 (m; C_6H_5), 6.85 (broad s; NH), 5.0–5.8 (m; $CH{=}CH_2$), 2.95 (s; CH_3), 2.85 (d, J = 6.4 Hz; CH_2). MS (70 eV): m/z = 230 (0.3 % M^+), 189 (100 % M–C_3H_5), 104 (78 %).

Microscale photolysis and preparation of the sample for HPLC

10 mg of barbiturate was dissolved in 1 ml of ethanol and 9 ml of carbonate buffer was added. 5 ml of this solution was placed in a cylindrical vessel (height 10 cm, vol. 25 ml) with the low pressure mercury arc NK 6/20 inside. The vessel was placed in an ultrathermostat and its content was irradiated for 15–60 min. The photolysate was extracted with 1 ml of CCl_4 and the organic phase was dried (Na_2SO_4) and evaporated in the air stream.

The residue was dissolved in 1 ml of EtOH and this solution was used for HPLC: column Ø 4.6/250 mm, Chromsil C18 10 μm; V_M = 2.7 ml; mobile phase: 10 % EtOH, 1 mM–NaH_2PO_4, 1 mM–Na_2HPO_4, 10 mM β-cyclodextrin; flow rate 1.1 ml/min; temp. 20°C; UV detector λ = 210 nm, injection vol. 5–10 μl).

References

1 H. Bartoń, A. Żurowska, J. Bojarski and W. Wełna, Pharmazie *38*, 268 (1983).
2 H. Bartoń, J. Bojarski and J. Mokrosz, Tetrahedron Lett. *1982*, 2133.
3 J. Knabe, H. Junginger and W. Geismar, Liebigs Ann. Chem. *739*, 15 (1970).
4 J. Knabe and D. Strauss, Arch. Pharm. (Weinheim) *305*, 54 (1972).
5 J. Knabe, W. Rummel, H. P. Büch and N. Franz, Arzneim. Forsch. *28*, 1048 (1978).
6 J. Knabe and W. Wunn, Arch. Pharm. (Weinheim) *313*, 538 (1980).
7 D. Sybilska, J. Żukowski and J. Bojarski, J. Liquid Chromatogr. in press.
8 J. Knabe, private communication.
9 D. O. Cowan and R. L. Drisko, Elements of Organic Photochemistry, p. 143, Plenum Press, New York 1976.

[Ph 75]

Arch. Pharm. (Weinheim) *319*, 461–465 (1986)

Resolution of Optical Isomers by Thin-Layer Chromatography

Enantiomeric Purity of D-Penicillamine

Jürgen Martens*)++), Kurt Günther+) and Maren Schickedanz+)

+) Fachbereich Forschung Chemie, Degussa AG, Hanau, and
++) Koordination Pharma, Degussa AG, Postfach 110533, D 6000 Frankfurt a.M. 11
Eingegangen am 24. April 1985

Penicillamine (**1**) is condensed with formaldehyde to form the enantiomeric 5,5-dimethylthiazolidinecarboxylic acids D-**3** and L-**3**. These enantiomers are separated by TLC on CHIRALPLATE®.

Dünnschichtchromatographische Enantiomerentrennung, Enantiomere Reinheit von D-Penicillamin

Es wird ein einfaches Verfahren zur Bestimmung der enantiomeren Reinheit von D-Penicillamin (D-**1**) beschrieben. Dazu wird **1** mit Formaldehyd zu **3** umgesetzt. Die Enantiomere von **3** lassen sich dc bei kurzen Analysezeiten trennen. Dabei kommt die mit einem optisch aktiven Selektor belegte Fertigplatte CHIRALPLATE® zum Einsatz.

Owing to its conceptual simplicity and manfested utility, the direct chromatographic separation of enantiomers upon chiral columns has been attempted many times. For most workers, the target has proven chimerical and, not withstanding the achievements of *Bayer*[1], *Blaschke*[2], *Cram*[3], *Gil-Av*[4], *König*[5], *Lochmüller*[6], *Pirkle*[7], and *Schurig*[8], there has been little portent development of broad spectrum chiral stationary phases of extended scope and utility. While no single chiral stationary

0365-6233/86/0505-0461 $ 02.50/0