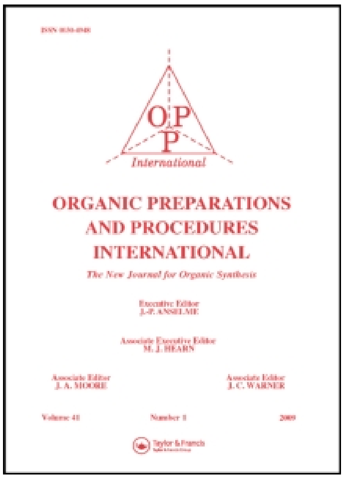


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF METABOLITES OF PHENOBARBITAL AND MEPHOBARBITAL

Abraham Philip[a]; F. I. Carroll[a]
[a] Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina

To cite this Article Philip, Abraham and Carroll, F. I.(1975) 'SYNTHESIS OF METABOLITES OF PHENOBARBITAL AND MEPHOBARBITAL', Organic Preparations and Procedures International, 7: 3, 117 — 122
To link to this Article: DOI: 10.1080/00304947509355130
URL: http://dx.doi.org/10.1080/00304947509355130

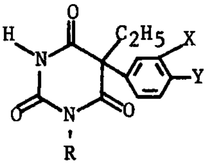
ORGANIC PREPARATIONS AND PROCEDURES INT. 7(3), 117-122 (1975)

SYNTHESIS OF METABOLITES OF PHENOBARBITAL AND MEPHOBARBITAL[1]

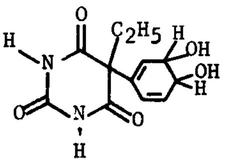
Abraham Philip and F. I. Carroll*

Chemistry and Life Sciences Division
Research Triangle Institute
Research Triangle Park, North Carolina 27709

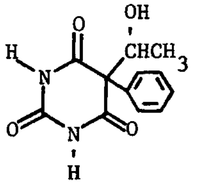
5-Ethyl-5-phenylbarbituric acid (Ia, phenobarbital) and 5-ethyl-1-methyl-5-phenylbarbituric acid (Ib, mephobarbital) are metabolized in man and animals to give 5-ethyl-5-(*p*-hydroxyphenyl)barbituric acid (Ic), 5-(3,4-dihydroxyphenyl)-5-ethylbarbituric acid (Id), 5-(3,4-dihydroxy-1,5-cyclohexadienyl-1-yl)5-ethylbarbituric acid (II) and 5-(1-hydroxyethyl)-5-phenylbarbituric acid (III).[2] In this paper, we describe the first



Ia, X = Y = R = H
Ib, X = Y = H; R = CH_3
Ic, X = R = H; Y = OH
Id, X = Y = OH; R = H

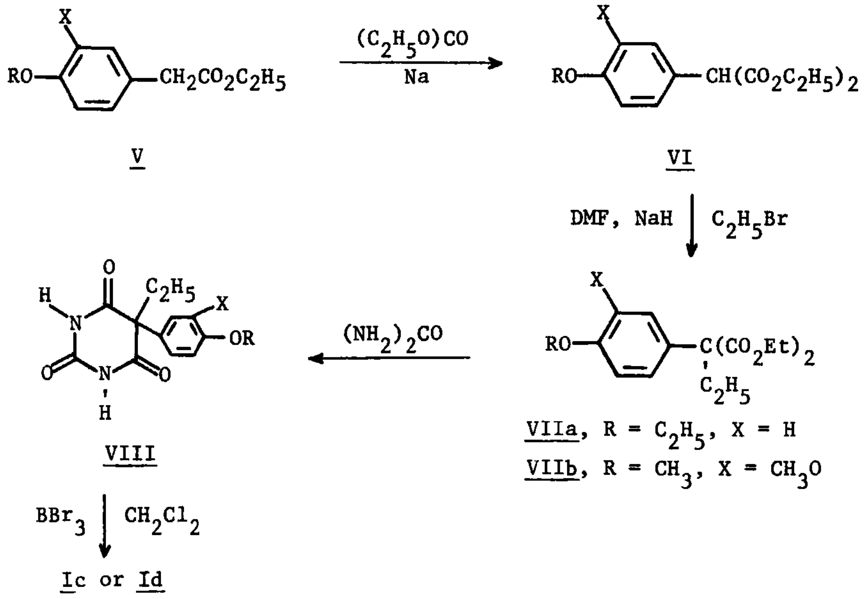


II



III

synthesis of Id and a new and improved procedure for the preparation of Ic. The reported synthesis of Ic[3] involving the sequence Ia → 5-ethyl-5-(*p*-nitrophenyl)barbituric acid (IVa) → 5-(*p*-aminophenyl)-5-ethylbarbituric acid (IVb) → Ic, suffers from the fact that the nitration of phenobarbital gives only 10-12% of the *p*-nitro isomer IVa, the major product being the *m*-isomer. In order to overcome this difficulty and to provide a general route whereby the dihydroxy metabolite Id could be obtained, we have prepared Ic and Id by the route shown below. Dealkylation of VIIIa



and VIIIb with boron tribromide in methylene chloride gave excellent yields of the desired metabolites Ic and Id respectively. The structure of Ic was verified by direct comparison to an authentic sample. The structure of both Ic and Id is supported by elemental analyses and spectral data which are presented in the experimental section.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage miscroscope using a calibrated thermometer. IR spectra were measured with a Perkin Elmer Model 467 Grating Infrared Spectrophotometer. Nmr spectra were recorded on a Varian Model HA-100 spectrometer with tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois.

Diethyl p-ethoxyphenylmalonate (VIa). - Sodium (0.92 g, 0.04 g-atom) was added in small pieces to a solution of 8.32 g (0.04 mol) of ethyl p-ethoxyphenylacetate (Va) in 60 ml of diethyl carbonate. On heating to 100° the reaction became exothermic. After the exothermic reaction had subsided, the mixture was heated under reflux for 1 hr. The excess diethyl carbonate was removed under vacuum. The remaining residue was diluted with 100 ml of cold water, neutralized with glacial acetic acid and extracted with ethyl ether (3 x 50 ml). The dried (Na_2SO_4) extracts were concentrated to a liquid which was distilled under reduced pressure through a 4 inch Vigreux column to give 7.2 g (64%) of VIa, bp 145-148° (0.4 mm).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19.
Found: C, 64.31; H, 7.22.

Diethyl 3,4-dimethoxyphenylmalonate (VIb). - In a manner analogous to that described for the preparation of VIa, 11.2 g (0.05 mol) of Vb was converted to 10.4 g (70%) of VIb, bp 165-167° (0.4-0.5 mm).

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80.
Found: C, 60.87; H, 6.88.

Diethyl alkoxylphenylethylmalonate (VII). - To a stirred suspension of 0.025 mol of 50% sodium hydride disperion in oil (hexane washed) in 10 ml of dry dimethylformamide was added 0.025 mol of VIa or VIb in 10 ml dimethylformamide. The solution was added dropwise at a rate to control hydrogen evolution. After the addition, the mixture was stirred until hydrogen evolution ceased. A total of 10 g (0.1 mol) of ethyl bromide was added in small portions over a 1 hr period, and the resulting mixture was stirred at 25° for 16 hr. The reaction was diluted with two volumes of water and extracted with ethyl ether (3 x 50 ml). The ethereal extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and dried under high vacuum at 50° to give VIIa and VIIb in 98 and 95% yields as light tan liquids. These products were used to prepare VIIIa and VIIIb respectively without further purification.

5-(*p*-Ethoxyphenyl)-5-ethylbarbituric Acid VIIIa). - A mixture of 1.54 g (0.005 mol) of VIIa, 1.5 g of urea and 1.13 g (0.010 mol) of potassium *t*-butoxide in 30 ml of dimethyl sulfoxide was stirred at room temperature overnight. The mixture was diluted with cold water and extracted with ethyl ether. The remaining aqueous layer was adjusted to pH 2 with 6N hydrochloric acid and extracted with ethyl ether (3 x 75 ml). The dried (Na_2SO_4) extracts were concentrated to a waxy solid. The solid was recrystallized from an EtOAc-C_6H_{14} mixture to give 0.90 g (65%) of VIIIa, mp 174-175°, nmr (Me_2CO-d_6) δ 0.92 (t, 3 $C\underline{H}_3CH_2C$–), 1.33 (t, 3, $C\underline{H}_3CH_2O$), 2.35 (q, 2, –$C\underline{H}_2CH_3$), 4.25 (q, 2, $OC\underline{H}_2CH_3$) and 7.08 ppm (two d, 4H ArH).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14.
Found: C, 60.69; H, 5.81; N, 10.16.

5-(3,4-Dimethoxyphenyl)-5-ethylbarbituric Acid (VIIIb). - The title compound was prepared by a procedure analogous to that described for the preparation of VIIIa. From 3.24 g (0.01 mol) of VIIb, 1.5 g (59%) of VIIIb was obtained. The compound recrystallized from EtOAc-C_6H_{14} had mp 157-158°; Lit.[5] mp 165-166°, nmr (Me_2CO-d_6) δ 0.93 (t, 3, $C\underline{H}_3CH_2$), 1.36 (q, 2H, $\underline{CH_2}CH_3$), 3.77 (s, 6, CH_3O) and 6.94 ppm (m, 3, ArH).

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.57.
Found: C, 57.37; H, 5.64; N, 9.73.

5-Ethyl-5-(*p*-hydroxyphenyl)barbituric Acid (Ic). - To a suspension of 200 mg (0.73 mmol) of VIIIa in 5 ml of methylene chloride cooled in a dry ice-acetone bath, a solution of 0.5 ml of BBr_3 in 5 ml of methylene chloride was added dropwise. The reaction mixture was allowed to warm to room temperature after the mixture became homogenous. The excess boron tribromide and methylene chloride were removed under a stream of nitrogen, and the remaining residue was heated with 5 ml of 6N HCl. The precipitate that formed on cooling was separated, washed with cold water and recrystallized from an EtOAc-C_6H_{14} mixture to give 160 mg (89%) of Ib 0.5 water, m.p. 214-215°; Lit.[3,4] mp 225-226°; uv (pH 9.02) λ_{max} 237 nm (ε 13,300) and λ_{sh} 280 nm (ε 200); nmr (Me_2CO-d_6) δ 0.91 (t, 3, $C\underline{H}_3CH_2$—), 2.35 (q, 2, $C\underline{H}_2CH_3$) and 7.2 ppm (two d, 4, ArH); the mass spectrum showed a m/e at 248 for the molecular ion.

Anal. Calcd. for $C_{12}H_{12}N_2O_4 \cdot 0.5\ H_2O$: C, 56.02; H, 5.09; N, 10.87.
Found: C, 56.03; H, 5.11; N, 11.00.

5-(3,4-Dihydroxyphenyl)-5-ethylbarbituric Acid (Id). - A 303 mg (1.13 mmol) sample of VIIIb was converted to 220 mg (74%) of Ic in a manner analogous to that described for the preparation of Ib. The compound Ib has mp 213-214°; uv (pH 9.02) λ_{max} 242 (ε 12,800) and 288 nm (ε 4,900); nmr (Me_2CO-d_6) δ 0.89 (t, 3, $C\underline{H}_3CH_2$), 2.30 (q, 2, —$C\underline{H}_2CH_3$) and 6.88 ppm (m, 3H, ArH).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.60.
Found: C, 54.37; H, 4.59; N, 10.72.

REFERENCES

1. This work was carried out under Contract No. PH-43-1057 with the Pharmacology-Toxicology Program, National Institute of General Medical Sciences, National Institutes of Health.

2. (a) D. J. Harvey, L. Glazener, C. Stratton, J. Nowlin, R. M. Hill and M. C. Horning, Res. Comm. Chem. Pathol. Pharmacol., 3, 557 (1972). (b) C. R. Craig and F. E. Shideman, J. Pharmacol. Exp. Ther., 176, 35 (1971). (c) L. C. Mark, Clin. Pharma. Ther., 4, 504 (1963) and references cited. (d) M. T. Bush and E. Saunders, Ann. Rev. Pharmacol., 7, 57 (1966) and references cited.

3. T. C. Butler, J. Pharmacol. Exp. Ther., 113, 226 (1955).

4. An authentic sample of 5-(p-hydroxyphenyl)-5-ethylbarbituric acid obtained from Dr. Butler had mp 215-216°. The mp of a mixture of our sample and Dr. Butler's sample had mp 215-216°.

5. A. Brossi, A. Focella, A. I. Rachlin and S. Teitel, S. African Patent 6,800,908; C.A., 70, 78000q (1969).

(Received February 6, 1975; in revised form June 16, 1975)