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# SYNTHESIS OF NEW PHASE- 1 METABOLITES OF TWO BARBITURATES

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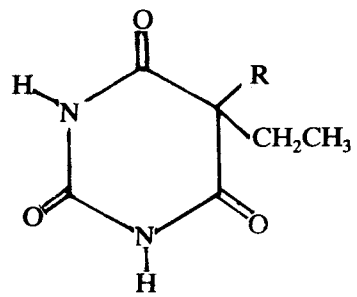
**Abstract**

The new 4'- hydroxy and 3'- aldehyde phase- 1 metabolites of butobarbitone and pentobarbitone are fully synthesized for the first time. These metabolites were used to idenfity and quantify the natural metabolites in human urine after single and multiple doses of these drugs. The synthesized metobolites have spectral characterizations (IR, NMR, U.V. and mass spectroscopy) consisted with the assigned structures.

## Introduction

The barbiturates hypnotics which have a straight side- chain like butobarbitone (**1**) and pentobarbitone (**2**) are metabolized to give phase- I metabolites which result from oxidation at the ($\omega$) or ($\omega$-1) positions of the butyl or pentyl side- chain. The known metabolites of butobarbitone and pentobarbitone include 3'- hydroxy, 3'- oxo (keto) and 3'- carboxyderivatives which were identified in human urine [1, 2, 3, 4].

Two new metabolites the 4'- hydroxy (terminal) and 3'- aldehyde derivatives of these two drugs were synthesized in this study.



compound **1** ⟶ R=-Bu (-$CH_2$ $CH_2$ $CH_2$ $CH_3$)
compound **2** ⟶ R=- (CH $CH_2$ $CH_2$ $CH_3$) $CH_3$

**Key words:** Barbiturates, metabolites, synthesis

The aim of the synthesis was to use these new compounds to identify and qualify these possible natural metabolites in human urine after oral administration of these drugs. In fact, these metabolites were identified and quantified in human urine using gas chromatography- mass spectrometry (GC- MS) technique.

## Results and Discussion

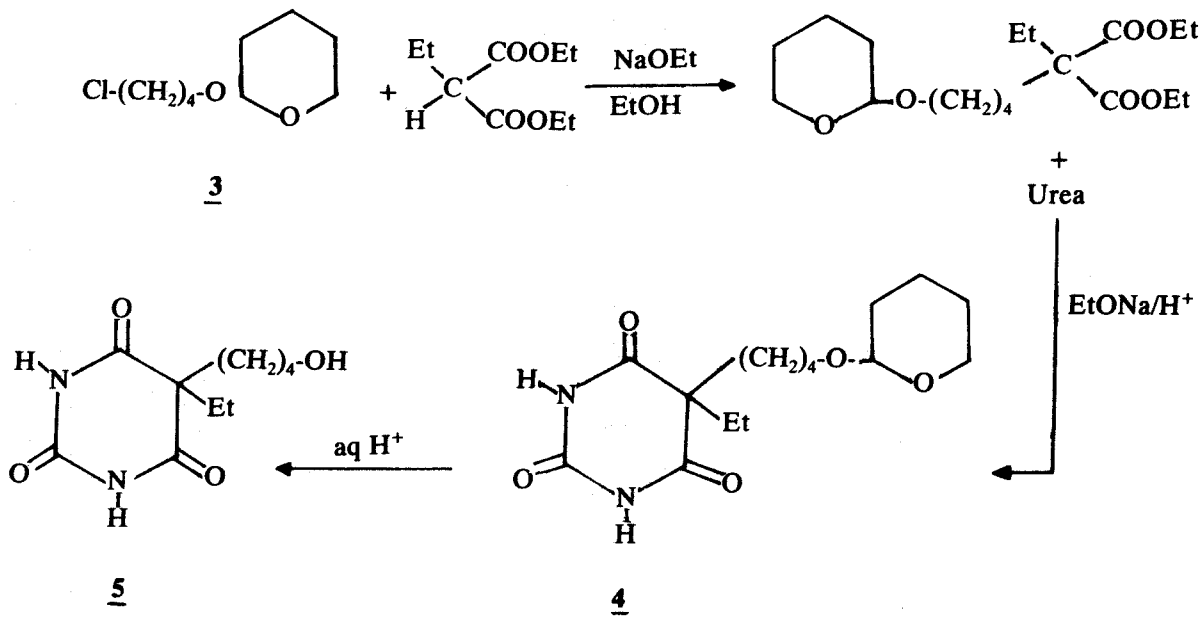
### A. Butobarbitone Metabolites:

In an attempt to synthesize 4'- hydroxy butobarbitone, 4- chlorobutanol was prepared by opening the ring of tetrahydrofuran [5] with hydrochloric acid gas, and then reacting the 4- chlorobutanol with diethyl ethylmalonate in the presence of NaOEt. The product diethyl ethyl (4- hydroxy butylmalanate) was cyclized [6] with urea to give 4'-hydroxybutobarbitone.

Unfortunately, the presence of NaOEt during the cyclization caused much of the 4- chlorobutanol to recyclize to tetrahydrofuran. As a result, the yield of the above compound was extremely low.

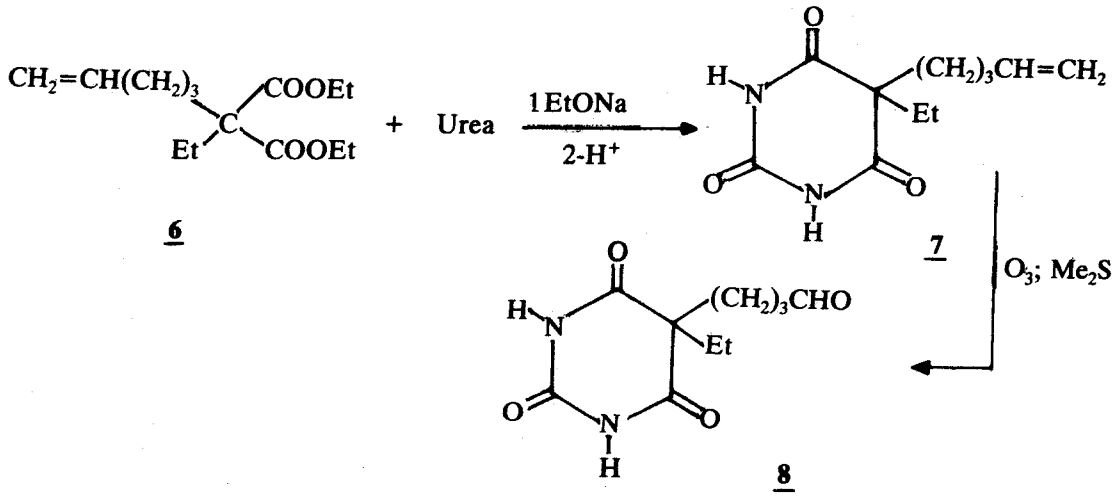
After modification by protecting the hydroxyl group of 4- chlorobutanol with 2, 3- dihydro- 4H- pyran, this route was followed again.

In this synthesis 1 (2- tetra hydropyranoxy)- 4- chlorobutane (3) was added to diethyl ethylmalanate and the product then cyclized with urea in the presence of NaOEt, followed by acidification to yield the protected 4'- hydroxybutobarbitone (**4**). The removal of the protecting group by acid hydrolysis gave the pure 4- hydroxy- butobarbitone (**5**).




The terminal aldehyde (4′- oxobutobarbitone) was prepared by cyclization of diethyl ethyl pent- 4′-enylmalonate (**6**) with urea under alkaline conditions, followed by acidification to yield 5- ethyl- 5 (pent- 4′-enyl) barbituric acid (**7**).

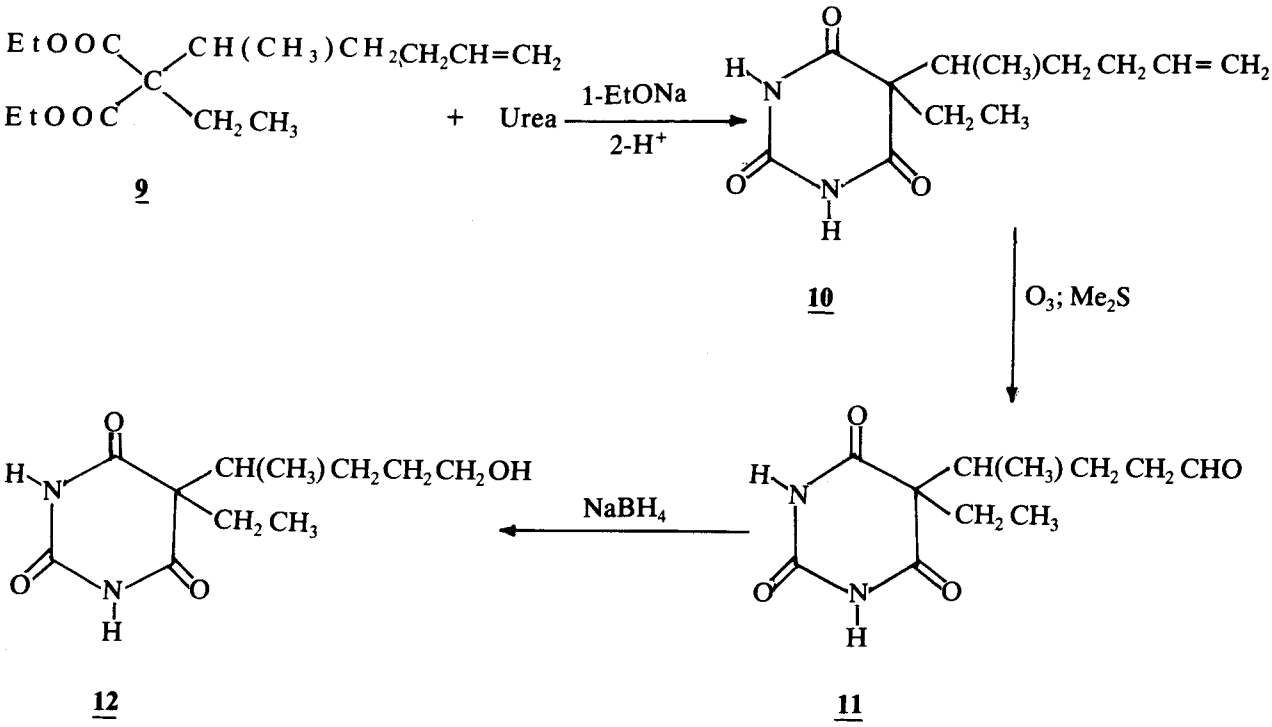
Ozonolysis of compound (**7**) in methanol at low temperature (-60°C) followed by workup in the presence of dimethyl sulphide yielded 3′- carboxybutobarbitone (4′- oxobutobarbitone) (**8**). This new compund showed a steady deterioration on storage, due to the general oxidation to the corresponding acid.



## B. Pentobarbitone Metabolites:

4'- Hydroxypentobarbitone (**12**) was prepared by the reduction of 3'-aldehydepentobarbitone(**11**)with sodium borohydride. The aldehyde was obtained by the scheme of synthesis similar to that used to prepare **8**.

(±)- 5- Bromohex- 1- ene was reacted with diethyl ethylmalonate to give diethyl ethyl (1- methylpent- 4- enyl) malonate (**9**), which was cyclized with urea as described before, to yield 5- ethyl- 5- (1'- methyl pent- 4- enyl) barbituric acid (**10**).




Ozonolysis of compound (**10**), followed by workup in the presence of dimethyl sulphide, afforded 4'- oxo pentobarbitone (3'- aldehydpentobarbitone) (**11**). A smooth reduction of the aldehyde with $NaBH_4$ in ether yielded a hydroscopic solid, the 4'- hydroxypentobarbitone (**12**).

## Experimental Section

### A. Butobarbitone metabolites synthesis:

**1- (2- Tetrahydropyranoxyl)- 4- chlorobutane (3)**

Hydrochloric acid (0.5 Ml) was added [6] dropwise to a mixture of 4- chlorobutanol (21.6 g, 0.2 mol) and 2.3- dihydro- 4H- pyran (16.8 g, 0.2 mol) and the mixture was stirred (2h, 20°C). Sodium hydroxide (ca. 0.1 g) was added to the mixture, which was then distilled, the product was collected at 95°C, 0.2 mmH (27 g. 71%). m/z 192 (M+), IR (film) $\nu$ max. 2950 (C-H), 1100 (C-O-C), on absorption near 3000- 3600 $cm^{-1}$ (O-H). NMR (CD $Cl_3$) $\delta$ 4.58 (q, 1H), 3.60 (m, 6H) 1.75 (m, 10H).

**Diethyl 4- (2- tetrahydropyranoxyl) butylethylmalonate**

Diethyl ethylmalonate (18.8 g, 0.1 mol) was added dropwise to hot (80 C) ethanolic sodium ethoxide [from sodium (2.8 g, .12 mol) in dry ethanol (60 ml)]. 1- (2- Tetrahydropyranoxyl)- 4- chlorobutane (19.2 g, 0.1 mol) was added dropwise (20 min), and heating was continued for 3h. the mixture was cooled, diluted with water (50 ml) and extracted with chloroform (2× 50 ml). The chloroform layers were dried and evaporated to give the product as a liquid (25 g, 73%). IR (film) $\nu$ max 2950 (C-H), 1730 (C=O), 1200 (C-O-C), noabsorption near 3000- 3600 cm (O-H) NMR (CD $Cl_3$) $\delta$ 4.60 (q., LH), 4.20 (q, 4H), 3.50 (m, 4H), 0.40 (m, 23H).

**4- Hydroxybutobarbitone (5)**

Sodium ethoxide was prepared [6, 7] by dissolving sodium (1.66 g, 72 m mol) in dry ethanol (50 ml), and then diethyl 4- (2'- tetrahydropyranoxy) butyl ethylmalonate (10.32 g, 30 m mol) and urea (2.16 g, 36 m mol) were added. The ethanol was distilled. The residue was dissolved in water (20 ml) and extracted with dichloromethane (10 ml), and the aqueous layer was acidified with conc. HCl, and extracted with ethyl acetate (3× 30 ml). The organic layer was dried and evaporated to a syrup (5g), which was dissolved in water (90 ml) ethanol (30 ml) and conc. HCl (1 ml) and the mixture was heated (80°C, 2h). The mixture was extracted with ethyl acetate (3× 50 ml), and the extract was dried and concentrated to a syrup which was crystallised from ethyl acetate to yield 4'- hydroxybutobarbitone (1.5 g, 22%) m.p. 108- 110°C, IR (Nujol) $\nu$ max 3500 (O-H), 3250 (N-H) 2900 (C-H), 1750, 1700 $cm^{-1}$ (C=O) NMR (Acetone-$d_6$) $\delta$ 10.20 (bs, 2H), 3.50 (t, 2H), 1.90 (m, 7H), 1.40 (q, 2H), 0.80 (t, 3H), Anal calcul for $C_{10}H_{16}N_2O_4$. C, 52.6, H, 7.5, N, 12.3. Found: C, 52.3, H, 7.1, N, 12.2.

**Diethyl ethylpent- 4- enylmalonate (6).**

Diethyl ethylmalonate (18.8 g, 0.1 mol) was added dropwise to a stirred solution of sodium ethoxide [sodium (2.3 g, 0.1 mol) in dry ethanol (50 ml)]. The mixture was heated under reflux (30 min) then 1-bromo- pent- 4'- ene (22.4 g, 0.15 mol), was added dropwise, and the whole mixture was heated under reflux (3h). The mixture was cooled and filtered, and the filtrate was evaporated (rotary- evaporator), the residue was distilled (170°C, 5m mHg) to give the pure product (7.25 g, 33%) IR (film) $\nu$ max 3080 (C=C), 2960 (C-H), 1720 (C=O), 1640 (C=C), 1200 (C-O-C), 990, 915 $cm^{-1}$ (R-CH=$CH_2$). NMR ($CDCl_3$) $\delta$ 5.80 (m, IH), 5.00 (m, 2H), 3.90 (m, 7H), 1.20 (t, 6H), 0.80 (m, 4H).

**5- Ethyl- 5- (pent- 4- enyl) Barbituric Acid (7)**

A mixture of diethyl ethyl pent- 4'- enyl malonate (6.49, 25 mmol) and urea (1.8 g, 30 mmol) in a solution of sodium (1.38 , 60 mmol) in dry ethanol (20 ml) was distilled until no more ethanol was obtained. The solid residue was dissolved in water (50 ml) and extracted with dichloromethane (2× 20 ml). The aqueous solution was acidified with conc. HCl and then extracted with ethyl acetate (3× 50 ml). The organic extract was dried and evaporated to a thick syrup which was crystallised and recrystallised from ethyl acetate to yield as colourless crystals the title compound (4.5 g, 80%) m. p. 123°C, IR (Nujol) $\nu$ max 3200 (N-H), 2900 (C-H), 1700 (C=O), 995 $cm^{-1}$ (R-OH=$OH_2$). NMR (Acetone-$d_6$): $\delta$ 10.00 (b s, 2H), 5.80 (m, 1H), 4.80 (m, 2H), 1.90 (m, 6H), 1.40 (m ,2H), 0.90 (t, 3H).

**5- (4'- Oxobutyl) 5- ethyl Barbituric Acid (8)**

5- Ethyl 5- (pent- 4- ethyl) barbituric acid (2.24 g, 10 mmol) in methanol (30 ml) was cooled (-60°C), and then ozonized with oxygen containing 28 of ozone per litre was passed through the solution (50 1/h). After about 3h, the mixture was flushed with nitrogen for 15 min, and then dimethyl sulphide (2 ml) was added [7]. The mixture was stirred at- 60°C for 2H and then at- 10°C for 1h and finally at room temperature for 1h. The mixture was concentrated, and the residue was dissolved in water (20 ml) and extracted with ethyl acetate (3× 30 ml). The extract was dried and evaporated to a thick syrup which was crystallised from ethyl acetate to yield as colourless crystals, **5- (4'- oxobutyl) 6- ethylbarbituric acid** (0.5 g, 0.22%) m. p. 125°C, IR (Nujol) $\nu$ max 3200 (N-H), 2920 (C-H), 1710 $cm^{-1}$ (C=O) NMR (Acetone- $d_6$) $\delta$ 10.20 (b s, 2H) , 9.70 (t, 1H), 2.50 (t, 2H), 1.80 (m, 6H), 1.20 (t, 3H). G. C. and t. l. c. showed that the product contains about 10% of 3'- carboxybutobarbitone.

**B. Petobaritone metabolites synthesis:**

**Diethyl Ethyl (1- Methyl pent- 4- enyl) malonate (9):**

Diethyl ethyl malonate (18.8 g, 0.1 mol) was added dropwise to a solution of sodium ethoxide [sodium (2.5 g, 0.1 mole) in dry ethanol (60 ml)] heated under reflux, and then (+)- 5- bromohex- 2- ene (24.5 g, 0.15 mol) was added dropwise, and the mixture was heated under reflux (4h). The mixture was filtered, and the filtrate was concentrated, dissolved in water (30 ml), and extracted with chloroform (3× 50 ml). The organic layers were dried and evaporated to give a residue which was distilled to yield diethyl ethyl (1- methyl-pent- 4- enyl) malonate (**9**) (4.1 g, 15%) b. p 82°C at 1 mmHg IR (Film) $\nu$max. 3080 (-C=C-H), 2970 (C=O), 1640 (-C=C-), 1200 (C- O-C), 990, 915 $cm^{-1}$ (R-OH=$OH_2$, NMR ($CDCl_3$) $\delta$ 5.85 (m, 1H), 5.00 (m, 2H), 4.30 (q, 4H), 2.10 (m, 5H), 1.35 (t, 6H), 1.00 (m, 8H).

**5- Ethyl 5- (1'- Methyl pent- 4'- enyl) Barbituric Acid (10)**

Diethyl ethyl (1- methyl pent- 4- enyl) malonate (4.0 g, 15 mol), and urea (1.1 g, 18 mmol) were added to a solution of sodium ethoxide [sodium (0.8 g, 36 mol) in dry ethanol (30 ml)]. The mixture was distilled (oil bath, 120°C) until all the ethanol had been removed. The residue was dissolved in water (30 ml) and washed with dichloromethane (30 ml). The aqueous layer was

acidified with conc. hydrochloric acid, and extracted with ethyl acetate (3× 50 ml). The organic layer was dried and concentrated to yield a syrup which was crystallized and recrystallized from ethyl acetate to give 5- ethyl 5- (1′- methylpent- 4′- enyl) barbituric acid as colourless crystals (1.6 g, 46%) m.p. 100-120°C. IR (Nujol) $\nu$ max 3200 (N-H), 2940 (CH), 1740 (C=O), 990, 915 $cm^{-1}$ (R-$CH_2$). NMR (Acetone- $d_6$) $\delta$ 5.85 (m, 1H), 5.00 (m, 2H), 2.10 (m, 7H), 1.00 (t, 6H).

**5- Ethyl- 5- (1′- methyl- 4′- Oxobutyl) Barbituric Acid (11)**

A solution of 5- ethyl 5- (1- methylpent- 4- enyl) barbituric acid (**10**) (1.2 g, 5 mmol) in methanol (20 ml) was ozonolyzed as described for the preparation of 5- ethyl 5- (4′- oxobutyl) barbituric acid. Compound (**11**) was obtained as colourless crystals (0.8, 66%) m. p. 130- 132°C, Anal. Calcul. for $C_{11}H_{16}N_2O_4$. C, 55, H, 6.7, N, 11.6% found C, 53.2, H, 6.7, N, 11, IR (Nujol) $\nu$ max 2980 (C-H), 1760, 1720 (C=O), 1470 $cm^{-1}$ (C-H). NMR (Acetone- $d_6$) $\delta$ 10.25 (b s, 2H), 9.75 (t, 1H), 2.50 (m, 2H), 2.10 (m, 7H), 1.00 (t, 6H). G. C, Analysis of the methylated product showed the presence of about 10% of 5- ethyl 5- (1′- methyl- 3′- carboxypropyl)- barbituric acid, and showed retention times of 9.2, 8.6 min. for 5- ethyl- 5- (1′- methyl- 4′- oxobutyl) barbituric acid and 3′- carboxypentobarbitone.

**4′- Hydroxypentobarbitone (12)**

To a solution of 5- ethyl- 5- (1- methyl- 4′- oxobutyl) barbituric acid (0.24, 1 mmol) in dry ethanol (20 mol), sodium borohydride (40 mg) was added and the mixture was heated under reflux (3H). The mixture was evaporated, and dissolved in water (10 ml) and extracted with ethyl acetate (3× 20 ml). The organic extract was dried and evaporated to give a residue which was crystallised from ethyl actate to give, as a hydroscopic product, 4′- hydroxypentobarbitone (200 mg, 80%) m. p. 118- 120°C. IR (Nujol) $\nu$ max 3400 (C-H), 2960 (C-H), 1760 (C-O), 1470 $cm^{-1}$ (C-H). NMR (Acetone- $d_6$) $\delta$ 10.25 (b s, 2H), 3.53 (t, 2H), 3.20 (m, 2H), 2.10 (m, 6H), 1.10 (d, 3H). Anal. calcul. for $C_{11}H_{18}N_2O_4$: C, 54.5, H, 8.0, N, 11.5. Found: C, 54.6, H, 7.8, N, 11.0.

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