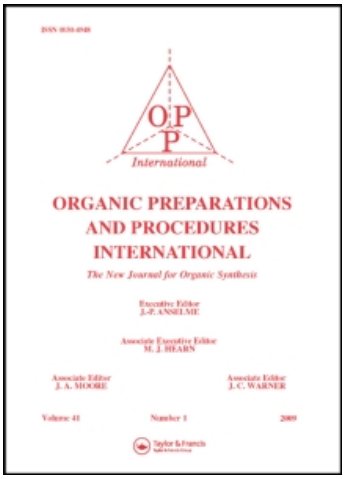


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# SYNTHESIS OF (*R*)-5-ALKYL-5-(1'-METHYL-3'-CARBOXYPROPYL) BARBITURIC ACIDS AND (*R*)-ALKYL-5-(1'-METHYL-3-CARBOXYPROPYL)-2-THIOBARBITURIC ACIDS

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# SYNTHESIS OF (R)-5-ALKYL-5-(1'-METHYL-3'-CARBOXYPROPYL)BARBITURIC ACIDS AND (R)-ALKYL-5-(1'-METHYL-3-CARBOXYPROPYL)-2-THIOBARBITURIC ACIDS

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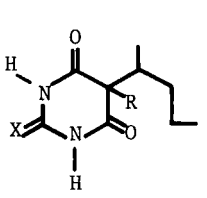
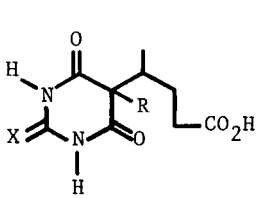
Recent reports from our laboratory as well as from elsewhere have demonstrated differences in the potency and in the rates of metabolism of the enantiomers of 5-ethyl-5-(1'-methylbutyl)barbituric acid (Ia, pentobarbital), 5-ethyl-5-(1'-methylbutyl)-2-thiobarbituric acid (Ib, thiopental) and 5-allyl-5-(1'-methylbutyl)-2-thiobarbituric acid (Ic, thiamylal).[1-7] 5-Ethyl-5-(1'-methyl-3'-carboxypropyl)barbituric acid (IIa), 5-ethyl-5-(1'-methyl-3'-carboxypropyl)-2-thiobarbituric acid (IIb), and 5-allyl-5-(1'-methyl-3'-carboxypropyl)-2-thiobarbituric acid (IIc) are important metabolites of Ia-c.[8,9] Although the synthesis of racemic IIa and IIb has been reported,[10,11] no syntheses of racemic IIc or any of any of the optical isomers of IIa-c have been reported. This paper presents methods for the syntheses of the (R)-isomers of IIa-c.



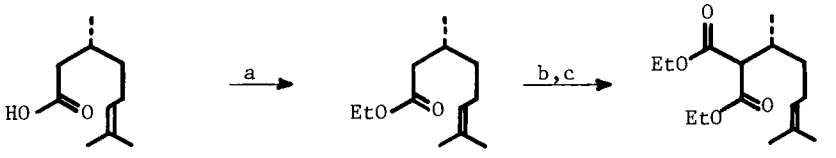
I



II

a, R = $C_2H_5$, X = O
b, R = $C_2H_5$, X = S
c, R = $C_3H_5$, X = S

(R)-Diethyl 1,5-dimethyl-4-hexenylmalonate (V), which serves as an intermediate for the synthesis of IIa-c, was prepared from the readily available optically pure citronellic acid (III)[12] as shown on the next page.

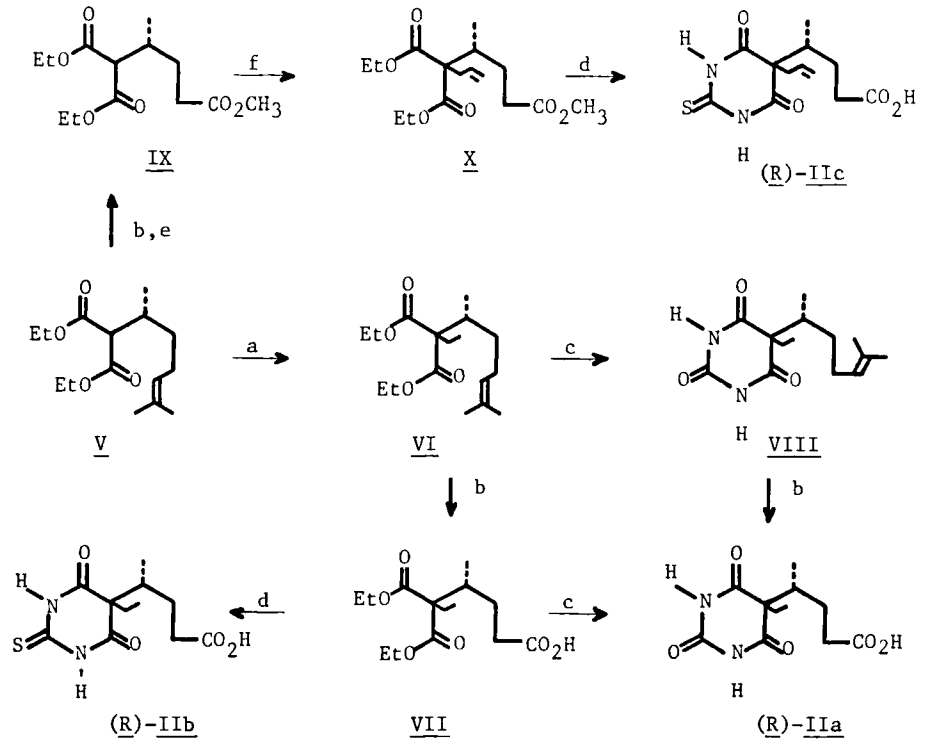


III IV V

a) EtOH, $H_2SO_4$ b) $(CO_2Et)_2$, EtONa c) heat

Treatment of IV obtained by esterification of III with diethyl oxalate in the presence of sodium ethoxide followed by thermal decarbonylation of the product obtained gave V.

The synthesis of (R)-IIa-c from V is depicted below. Alkylation of the sodium salt of V with ethyl iodide in DMF gave (R)-diethyl 1,5-dimethyl-4-hexenylethylmalonate (VI). Treatment of VI with



a) $C_2H_5I$, NaH, DMF b) $RuO_4$ c) $(NH_2)_2CO$, $K^+O^-tBu$, DMSO
d) $(NH_2)_2CS$, $CH_3O^-Na^+$, $CH_3OH$ e) $CH_2N_2$ f) $CH_2{=}CHCH_2Br$, NaH, DMF

ruthenium tetroxide gave (R)-diethyl 1-methyl-3'-carboxypropylethylmalonate (VII). Condensation of VII with urea in dimethylsulfoxide containing potassium tert-butoxide[13] or thiourea in methanol containing sodium methoxide[14] afforded the desired acids (R)-IIa and (R)-IIb, respectively. The acid (R)-IIa was also prepared by converting VI to (R)-5-ethyl-5-(1,5-dimethyl-4-hexenyl)barbituric acid (VIII) followed by ruthenium tetroxide oxidation. Careful oxidation of V with ruthenium tetroxide followed by esterification of the acid formed with diazomethane gave (R)-diethyl 1-methyl-3-carbomethoxypropylmalonate (IX). Treatment of the sodium salt of IX with allyl bromide in DMF gave (R)-diethyl 1-methyl-3-carbomethoxypropylallylmalonate (X). Condensation of X with thiourea in methanol containing sodium methoxide yielded the desired acid, (R)-IIc.



## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, IL.

(R)-Diethyl 1,5-Dimethyl-4-hexenylmalonate (V).— To a solution of 1.8 g (0.078 g-atom) of sodium metal in 50 ml of absolute alcohol was added 15 g (0.074 mol) of IV[15] followed by 30 g (0.2 mol) of diethyl oxalate at 50-60°C. and the mixture was kept at this temperature for 6 hr under reduced pressure by water aspiration to remove the alcohol generated. After cooling, the reaction mixture was neutralized with 6.6 ml of glacial acetic acid and diluted with 150 ml water, and extracted with ethyl ether. The ether extract was washed with water, bicarbonate solution, water and dried ($Na_2SO_4$). After removing ether and excess of diethyl oxalate, the residue was heated at 160-170°C for 3 hr and then distilled to give 10.5 g (53%) of V; bp. 110 at 0.2 mg Hg, $[\alpha]_D^{25}$ -0.31° (c, 5.8, MeOH).

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.59; H, 9.63.

(R)-Diethyl 1,5-Dimethyl-4-hexenylethylmalonate (VI).— To a suspension of 0.5 g of sodium hydride (50% in white oil) in dry DMF was added dropwise 2.7 g (0.01 mol) of V until hydrogen evolution ceased. The mixture was stirred for another hour, and 2.32 g (0.015 mol) of ethyl iodide was added. After stirring for 16 hr, the reaction mixture was poured into 200 ml of ice water, extracted with ethyl ether, washed with water and dried ($Na_2SO_4$). After removal of ether, the residue was distilled to give 2.65 g (89%) of VI; bp. 98-100° at 0.1 mm Hg; $[\alpha]_D^{25}$ +3.13 (c, 3.55, MeOH).

Anal. Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: 68.39; H, 10.38.

(R)-Diethyl 1-Methyl-3-carboxypropylethylmalonate (VII).— A suspension of 300 mg of ruthenium dioxide in 15 ml acetone was stirred with a solution of sodium metaperiodate in 20 ml water until a yellow color developed. When a few drops of a solution of 5.6 g (0.019 mol) of VI in 50 ml of acetone was added, the dark color of $RuO_2$ developed. More of the sodium metaperiodate was added, and this alternate addition of VI and sodium metaperiodate continued over a period of 45 min. After 1 1/2 hr, 100 ml of isopropyl alcohol was added and stirring continued for another 30 min. The solid obtained after filtration was washed with acetone. The combined filtrate and washings were concentrated to a small volume and extracted with ethyl ether. The ether solution was extracted with sodium bicarbonate solution. After washing with ether, the basic solution was neutralized with 6N HCl and extracted with ethyl ether. The ether extracts were washed, dried ($Na_2SO_4$), and concentrated to give 3.8 g (70%) of VII as a syrupy liquid. This product was used without further purification.

(R)-Diethyl 1-Methyl-3-carbomethoxypropymalonate (IX).— Oxidation of 10.8 g (0.04 mol) of V with ruthenium tetroxide using a procedure similar to that described for the preparation of VII gave a syrupy liquid which was esterified with diazomethane in ether. The residue, after concentration, was distilled to give 7.12 g (65%) of IX, bp. 115-117°C at 0.1 mm, $[\alpha]_D^{24}$ +2.24° (c, 1.05 MeOH).

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.72; H, 8.06.

(R)-Diethyl Allyl-(1'-methyl-3'-carbomethoxypropyl)malonate (X).— Compound IX (11.7 g, 0.043 mol) was alkylated by a procedure similar to that used to alkylate V using NaH (2.13 g), DMF (10 ml), and allyl bromide (24.2 g, 2 mol) to give 9.7 g (72%) of X. Bp. 158-159° at 0.2 mm; $[\alpha]_D^{24}$ +16.94°C (c, 5.515, MeOH).

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 61.11; H, 8.34. Found: C, 61.08; H, 8.28.

(R)-5-Ethyl-5-(1',5'-dimethyl-4-hexenyl)barbituric Acid (VIII).— Compound VIII was prepared in 76% yield by a procedure similar to that used to prepare other barbituric acid derivatives,[13] mp. 81-82°.

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.00; H, 8.38; N, 10.48.

(R)-5-Ethyl-5-(1'-methyl-3'-carboxypropyl)barbituric Acid [(R)-IIa]

A. From VIII.— Oxidation of 0.5 g (0.0019 mol) of VIII with ruthenium tetroxide by a procedure similar to that used to prepare racemic IIa[10] gave 0.41 g (85%) of (R)-IIa, mp. 193-195°; $[\alpha]_D^{24}$ +13.0 (c 0.78, MeOH).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.48; H, 6.30; N, 10.78.

B. From VII.— Compound (R)-IIa was prepared in 15% yield from VII using a procedure similar to that described for the preparation of other barbi-

turic acid derivatives;[13] mp. 193-195°. This product was identical to (R)-IIa prepared in A above.

(R)-5-Ethyl-5-(1'-methyl-3'-carboxypropyl)-2-thiobarbituric Acid [(R)-IIb].— To a stirred solution of 0.76 g of sodium in 40 ml of dry methanol at 56-60°C was added 3.3 g (0.044 mol) of dried thiourea and 3.2 g (0.011 mol) of VII. After stirring overnight at 55-60°, the reaction mixture was concentrated at 30°C under reduced pressure, diluted with 50 ml of ice water, neutralized with acetic acid and extracted with ether (3x 100 ml). The extracts were washed with water and dried ($Na_2SO_4$). The residue obtained on concentration was chromatographed on silica gel using an ethyl acetate-chloroform gradient as eluent to give (R)-IIb. Recrystallization from ethyl acetate-hexane gave 0.60 g (20%). Mp. 180-181°; $[\alpha]_D^{24}$ +16.78 (c, 0.87 g, MeOH).

Anal. Calcd. for $C_{11}H_{16}O_4N_2$: C, 48.81; H, 5.92; N, 10.29; S, 11.78. Found: C, 45.51; H, 5.97; N, 10.29; S, 11.95.

(R)-5-Allyl-5-(1'-methyl-3'-carbonylpropyl)-2-thiobarbituric Acid [(R)-IIc].— A mixture of 4.71 g (0.015 mol) of X and 2.34 g (0.03 mol) of thiourea was added to a solution of 0.69 g (0.03 g-atom) of sodium in 30 ml of methanol, and the mixture was heated at 50-55° overnight. The mixture was worked up as described for the preparation of (R)-IIb to give a waxy residue which was chromatographed on silica gel using EtOAc/$CHCl_3$ as the eluent. Concentration of the product fractions and recrystallization from ethyl acetate-hexane gave 0.85 g (20%) of (R)-IIc. Mp. 78-79°; $[\alpha]_D^{23}$ +12.99° (c, 0.778, MeOH).

Anal. Calcd. for $C_{12}H_{16}N_2O_4S$: 50.69; H, 5.67; N, 9.85; S, 11.28. Found: C, 50.58; H, 5.63; N, 10.00; S, 11.30.

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