Synthesis of (1′*RS*,3′*SR*)- and (1′*RS*,3′*RS*)-5-Ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric Acid

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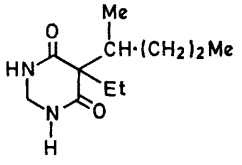
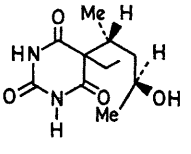
Summary The synthesis of (3*RS*,5*SR*)-*cis*- and (3*RS*,5*RS*)-*trans*-3,5-dimethylvalerolactone and their conversion into (1′*RS*,3′*SR*)- and (1′*RS*,3′*RS*)-5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acids, important biotransformation products of 5-ethyl-5-(2′-pentyl)barbituric acid (I), is reported, thus establishing the correct structural assignment of these hydroxylated metabolites of (I).

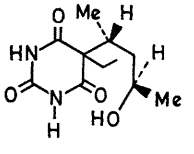
IN studies on the biotransformation of (*RS*)-5-ethyl-5-(2′-pentyl)barbituric acid (I),† Maynert and Dawson isolated the two diastereoisomeric pairs of 5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acid (II).[1] Since this initial report, there has been a continuing interest in the metabolism of (*RS*)-(I) and in the chemistry of its metabolites. The metabolism of (*RS*)-(I) has recently been repeated, and in



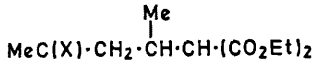
(I)



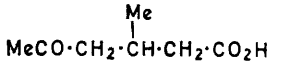
(IIA)



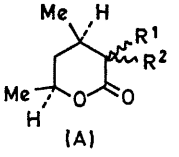
(IIB)



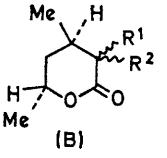
(III) X = O=
(IV) X = -O(CH$_2$)$_2$O-



(V)



(A)



(B)

(VI) R^1 = R^2 = H
(VII) R^1 = CO_2Et, R^2 = H
(VIII) R^1 = CO_2Et, R^2 = Et

addition the four optical isomers of (II) have been isolated from the metabolism studies of optically pure (*R*)-(+)-(I) and (*S*)-(−)-(I).[2,3] On the basis of differences in physical and spectral properties, tentative structural assignments to the four pure isomers and thus to the diastereoisomeric pairs isolated from the metabolism of (*RS*)-(I) have been suggested. However, the stereochemistry of the asymmetric centres in the 3-hydroxy-1-methylbutyl side-chain of (II) have not been unequivocally defined. Since the metabolism of (*R*)-(+)-(I) and (*S*)-(−)-(I) give different amounts of their respective hydroxy-enantiomers[2,3] and since the pharmacological effect of the enantiomers of (I) are quite different,[4] the correct stereochemical assignment of these metabolites is of extreme importance. We now report a synthesis of the pure diastereoisomeric pairs of (II) that establishes the correct stereochemical assignment of these isomers.

Diethyl 1-methyl-3-oxobutylmalonate (III) obtained by the Michael addition of diethyl malonate to pent-3-en-2-one was converted into its ethylene acetal derivative (IV). Alkaline hydrolysis of (IV), followed by acidification and thermal decarboxylation, yielded 3-methyl-5-oxohexanoic acid (V). Catalytic reduction of an ethanol solution of (V) using platinum oxide gave a mixture of the (3*RS*,5*SR*)-*cis*- and (3*RS*,5*RS*)-*trans*-3,5-dimethyl-valerolactones (VI). These lactones were separated by preparative g.l.c. using a 15 ft × $\frac{3}{8}$ in copper column packed with 20% DEGS on 60/80 Chromosorb-W AW-DMCS (165°, flow rate 150 ml/min of helium). For isolation 30 μl samples were processed on this column until 0·40 g of (VIA) (ret. time 48 min; η_D^{25} 1·4445) and 0·26 g of (VIB) (ret. time 59 min 30 s, η_D^{25} 1·4476) had been collected. The stereochemical assignment of the lactones (VI) has been established by a detailed analysis of their n.m.r. spectra.[5]

A benzene solution of the lactone (VIA) was condensed with diethylcarbonate in the presence of sodium hydride to give the 2-ethoxycarbonyl derivative (VIIA). Treatment of a dimethylformamide solution of (VIIA) with iodoethane in the presence of sodium hydride afforded 2-ethoxycarbonyl-2-ethyl-3,5-dimethylvalerolactone (VIIIA). The condensation of VIIIA with urea under normal conditions gave (1′*RS*,3′*SR*)-5-ethyl-5-(3′-hydroxy-1′-methylbutyl)-barbituric acid (IIA),‡ m.p. 191—192°, u.v. (pH 10·7) λ_{max} 239 (ϵ 10,000). Similarly, lactone (VIB)‡ gave (1′*RS*,3′*RS*)-5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acid (IIB),‡ m.p. 145—147°, u.v. (pH 10·7) λ_{max} 239 (ϵ 10,100). This synthesis of (IIA) and (IIB) establish unequivocally the structure of the hydroxy metabolites of (*RS*)-(I).

By direct comparison it was found that the n.m.r. $(CD_3)_2SO$ spectra of (IIA) and (IIB) are identical to the spectra of the hydroxy-metabolites, 1*R*-II and 2*R*-II,§ respectively, isolated from the metabolism of (*R*)-(+)-(I). Based on differences in physical and spectral properties, the hydroxy-metabolites 1R-II and 2R-II of (R)-(+)-(I) were assigned the structures (1′*R*,3′*R*)-(II) and (1′*R*,3′*S*)-(II), respectively and the hydroxy-metabolites, 1*RS*-II and 2*RS*-II,§ of (*RS*)-(I) were assigned the structures (1′*RS*,3′-*RS*)-(II) and (1′*RS*,3′*SR*)-(II), respectively.[2] It is apparent from the spectral comparison above as well as a comparison of the physical properties of (IIA) and (IIB) with those of the metabolites 1R-II, 2R-II, 1RS-II and 2RS-II,§ that the original stereochemical assignments in both sets of metabolites should be reversed.[2]¶

† The generic name of this compound is pentobarbital.
‡ The structure of only one optical isomer is shown.
§ The names, metabolite 1R-II, 2R-II, 1RS-II, and 2RS-II refer to the designation used by Palmer and his co-workers.[2] Spectra of these compounds were provided by Dr. Palmer.
¶ Slight differences noted in the m.ps and i.r. (KBr) spectra of 1*RS*-II and 2*RS*-II are attributable to the fact that these metabolites contain unequal amounts of the enantiomers. The u.v. spectrum of 1*RS*-II shows a higher extension coefficient than 2*RS*-II whereas (IIA) and (IIB) have identical u.v. properties. The reason for this difference is not apparent.

Compound (IIA) is also identical with a sample of (II) prepared by the method of Dickert, Shea, and McCarty which uses totally racemic starting material.[6] This results from the fact that the crude sample of (II) isolated by these authors was purified by recrystallization from water. Compound (IIA) is considerably more insoluble in water than (IIB) and can be obtained in pure form from a mixture of (IIA) and (IIB) by recrystallization from water.

From more recent metabolism studies Maynert[7] isolated a compound which he described as identical with the synthetic (II) of Dickert, Shea, and McCarty, and designated the metabolite as the "*dd* + *ll*" forms of (II). Our results clearly show that this assignment is incorrect and that the so-called new metabolite is actually (IIA). The only difference between Maynert's "new metabolite" and metabolite (1)(*RS*) reported by Palmer[2] is the ratio of enantiomers present in each case.

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