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SYNTHESIS OF COMPOUND X, A NON-STEROIDAL CONSTITUENT OF FEMALE URINE, AND CONGENERS

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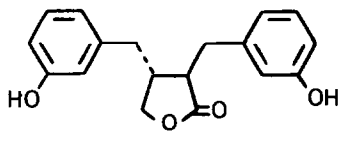
Summary : The synthesis of trans-(±)- and (-)-3,4-bis [(3-hydroxyphenyl) methyl] dihydro-2-(3H)-furanone (1), a recently discovered constituent of female urine, and some related compounds of biological interest is described.

During gaschromatographic analysis of urinary estrogens[1] Stitch and coworkers observed the persistent occurrence of an unknown component (Compound X)[2]. The periodic excretion of this compound with distinct maxima in the luteal phase of the menstrual cycle and during the first trimester of pregnancy suggested Compound X to have biological significance[2]. Recently the structure of Compound X was shown to be : trans-(±)-3,4-bis [(3-hydroxyphenyl) methyl] dihydro-2 (3H)-furanone (1)[3]. The same substance appears to be excreted by a monkey species (Cercopithecus Aethiopus Pygerythrus)[4].

The structure of 1 is most intriguing, since it bears a striking resemblance to some of the lignans[5], a group of natural products occurring in plants, but thus far not encountered in man or animal. Lignans recently have received a great deal of attention because many members show anti-tumour activity[5, 6], among which compounds 2 and 3[7]. Furthermore, while the resemblance of 1 with the natural estrogens is remote there is some similarity with synthetic non-steroidal estrogens, such as hexestrol (4).



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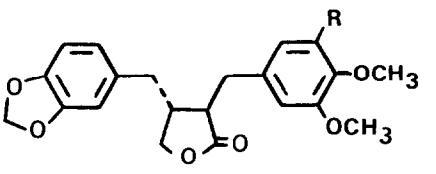
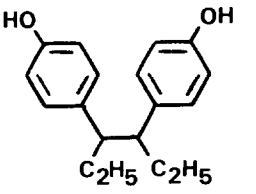


2 R=H

3 R=OCH3



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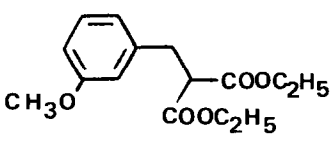
The potential biological activity of 1 prompts us to report its synthesis, which also should be

applicable to lignans with related structure. The diol 6[8], mp 81-82°C, easily obtained by reduction of the known diester 5[9], was converted into the monotosylate 7 (1 equiv. of NaH, p-TsCl, THF/HMPA, 20°C, 2h) and hence into the nitrile 8 (KCN, DMSO, 50°C). Hydrolysis of the nitrile with concomitant ring closure (conc. H_2SO_4/HOAc/H_2O 1:10:5, 110°C, 0.5h) produced the monosubstituted lactone 10 in 52% yield (based on 6) as an oil.



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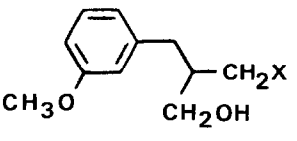
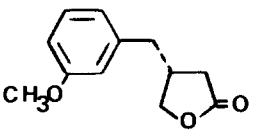


6 X = O 8 X = CN

7 X = OTs 9 X = COOH



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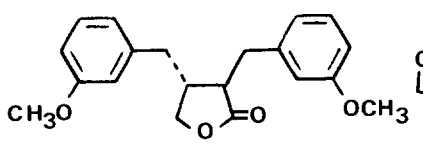
The anion of 10 was generated (i-Pr_2NLi, THF/HMPA, -70°C) and alkylated with m-methoxybenzylbromide (-70 to -50°C) to give 11 (oil) in 70-80% yield. Subsequent demethylation (BBr_3,CH_2Cl_2, 0°C) produced 1, mp 141-143°C, in 80% yield. This material was identical with Compound X of natural origin[2, 3].

When the lactone 10 was treated successively with aqueous base and acid the unstable hydroxy acid 9 was obtained, which was resolved via its salt with d-amphetamine. Acid treatment of the less-soluble diastereomeric salt, obtained by four recrystallizations from ethyl acetate, produced (+)-10, $[\alpha]_D^{20}$ = +6.4° (c=1, $CHCl_3$).

From this by the same sequence as described for the racemic compounds (-)-1 was obtained, mp 125-129°C, $[\alpha]_D^{20}$ = -38.4° (c=0.5, $CHCl_3$). The optical rotations of (+)-10 and (-)-1 compare favourably with those reported for the closely related lactones 12 ($[\alpha]_D^{20}$ = +4.8°[10a]; +5.22°[10b]) and 13 ($[\alpha]_D^{20}$ = -35°[11]) with known absolute configuration. Therefore most likely (-)-1 also has the 3R, 4R configuration (as depicted in the formula of 1).

Comparison of the specific optical rotation of (-)-1 with those found for samples of Compound X ($[\alpha]_D^{20}$ = -5° to 0°) shows that the latter is nearly racemic, the optical purity not exceeding ~13%. This virtually precludes the already unlikely



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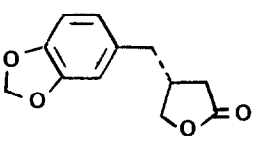

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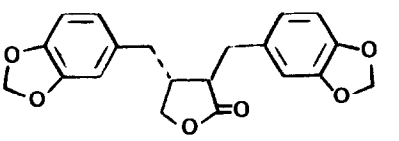

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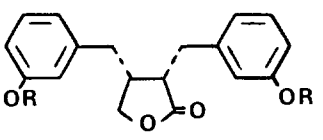
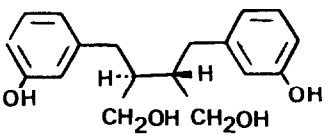
possibility that Compound X is somehow derived from lignans ingested with the diet, since in nature these occur in the optically pure 3R, 4R form only. While racemization at C-3 might occur such is not the case for the chiral centre at C-4, so that any optical activity present in compounds like 1 should be retained even under rigorous conditions. At the same time the absence of significant optical activity in Compound X suggests that it is not a primary product of biosynthesis, but rather a metabolite of an as yet unknown biologically relevant substance. Therefore some conceivable presursors of natural 1 were synthesized also.

Thus when 11 was refluxed with 25% KOH in 50% aqueous ethanol for three days a mixture of hydroxy acids was obtained. Fractional lactonization[12] gave starting material 11 (30% yield) and its cis-isomer 14 (29% yield). Demethylation of 14 (BBr_3, CH_2Cl_2, 0°C) produced 15, mp 157-158°C, in 70% yield; 200 MHz ^{1}H-NMR spectrum ($CDCl_3$) :



14 R=CH_3
15 R=H



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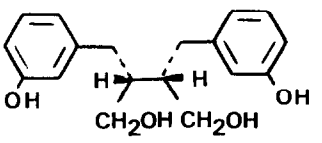

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δ 2.68 (m, H at C-4), 2.27 (dd, J= 13.5 & 12) and 2.92 (dd, J= 13.5 & 4, Ar$\underline{CH}_2$ at C-4), 2.75 (dd, J= 14.5 & 10.5) and 3.21 (dd, J= 14,5 & 4.5, Ar$\underline{CH}_2$ at C-3), 3.08 (ddd, J= 10.5, 7 & 4.2, H at C-3), 4.00 (ddd, J= 9, 4.5 & 0.7, H at C-5), 4.08 (dd, J= 9.2 & 2, H at C-5), 6.4 - 7.2 (m, 8, aromatic H's).

The ^{1}H-NMR spectral data of 15 are consistent with an envelope conformation of the lactone ring with the substituent at C-3 in a quasi-equatorial and the one at C-4 in a quasi-axial position[13]. Reduction of 1 ($LiAlH_4$, THF, 20°C, 2h) produced the (±)-diol 16, mp 171-173°, 60 MHz ^{1}H NMR (DMSO-d_6): δ 1.87 (m, 2, tertiary H's), 2.44 (m, 4, benzylic H's), 3,3 (d, J= 2.5, 4, 2x$\underline{CH}_2$OH) 6.4-7.1 (m, 8, aromatic H's). Similar reduction of 15 gave the meso-diol 17 as a viscous oil. Among the compounds 15-17 the last compound is the most likely candidate of being a precursor of Compound X, being inherently symmetrical. Investigation of the endocrinological and pharmacological properties of the compounds 1 and 15-17 is under way.

References and notes

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13. Reported ^{1}H-NMR spectral data of 1^{3} indicate that in this compound the lactone ring has a similar conformation, both substituents now being in a quasi-equatorial position

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