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SYNTHESIS OF CACALOL

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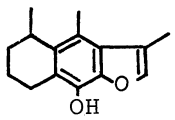
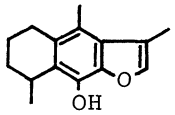
It is established that cacalol is 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-ol by synthesis in several steps from creosol methyl ether.

Cacalol is one of the major components isolated from the root of Cacalia decomposita A.Gray[1], a compositae widely distributed in the northern part of Mexico, and is related[2] by DDQ and subsequent chromic acid oxidations to maturinone, a co-component found in that plant. The structures of these compounds were assigned as IA and IIA, respectively, by their chemical and spectroscopic evidences[2,3].

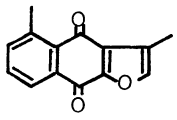
However, in 1969, we[4] and other two groups[5,6] have independently synthesized the quinone II and have found the identity of II with maturinone; and have proposed to revise the structure of cacalol to I.



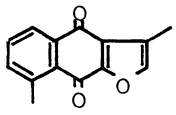
I



IA



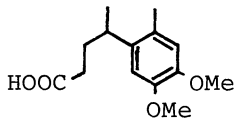
II



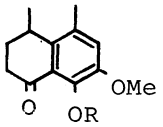
IIA

This communication deals with the synthesis of 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-ol(I) in order to clarify the structure of cacalol.

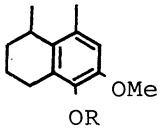
Friedel-Crafts reaction between creosol methyl ether and γ-valerolactone followed by the action of dimethyl sulfate on the acidic mixtures gave an acid III, $\delta(CDCl_3)$: 6.66(s, 1H), 6.70(s, 1H), as a single product in 75% yield. The acid was cyclized with phosphorus pentoxide-methanesulfonic acid[7] to afford a dimethoxytetralone IV, mp 100-103°C, $\nu(CHCl_3)$: 1670, 1585 cm^{-1} and $\delta(CDCl_3)$: 1.21(d, 3H, J=7Hz) 2.33(s, 3H), 3.83(s, 6H), 6.89(s, 1H), in 70% yield. When PPA(160°C) was used as a cyclizing agent, a mono-demethylated tetralone V, mp 57-61°C, which showed the characteristic absorption for the 8-hydroxy-1-tetralone moiety in IR and NMR spectra, $\nu(CHCl_3)$: 1630, 1590 cm^{-1} and $\delta(CDCl_3)$: 1.25(d, 3H, J=7Hz), 2.29(s, 3H), 3.86(s, 3H), 6.87(s, 1H), 12.94(s, 1H), was obtained in 28% yield. The conversion(74% yield) of the latter with dimethyl sulfate to the dimethoxytetralone IV confirmed the relation between two C-methyl groups as shown.



III



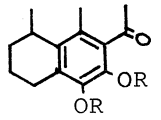
IV R=Me
V R=H



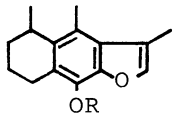
VI R=Me
VII R=Ac

A ketonic function in IV was removed by hydrogenolysis (10% Pd-C, AcOH, $HClO_4$) to give a dimethoxytetraline VI.

The introduction of an acetyl group at the remaining position of the aromatic ring was carried out by Friedel-Crafts acetylation (AcCl, $AlCl_3$, tetrachloroethane, 70°C), followed by treatment with dimethyl sulfate to give VIII (20% yield), $\nu(CCl_4)$: 1700 cm^{-1} and $\delta(CCl_4)$: 1.15(d, 3H, J=7Hz), 2.07(s, 3H), 2.38(s, 3H), 3.75(s, 3H), 3.78(s, 3H). The main product in this reaction was VII (53% yield), mp 68-69°C, $\nu(CHCl_3)$: 1750, 1600 cm^{-1}.



VIII R=Me
IX R=H
X R=CH_2COOMe



XI R=CH_2COOH
XII R=Ac

Treatment of the acetyl derivative VIII with boron tribromide in dichloromethane followed by potassium carbonate-methyl bromoacetate afforded X, mp 89-90°C, $\nu(CCl_4)$: 1765, 1745, 1700 cm^{-1}, via a dihydroxy compound IX.

The bis(methoxycarbonylmethyl) ether X was subjected to alkaline hydrolysis and subsequent cyclization with sodium acetate in acetic anhydride[8] gave a furan derivative XI, mp 168-169°C, $\delta(CDCl_3)$: 1.16(d, 3H, J=7Hz), 2.37(br.s, 3H), 2.50(s, 3H), 5.02(br.s, 2H), 7.14(br.s, 1H), in good yield.

The removal[9] of the carboxymethyl group was succeeded by successive treatment with lithium aluminium hydride, tosyl chloride in pyridine, sodium bromide in dimethyl sulfoxide and finally with n-butyl lithium. As the synthetic 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-ol(I), $\nu(CCl_4)$: 3660, 1220, 1107 cm^{-1}, thus obtained was hardly crystallized even after chromatographic purification, the comparison was done with its acetate XII, mp 119-120°C, which showed identical IR spectrum, $\nu(CCl_4)$: 1760, 1192, 1100 cm^{-1}, with that of authentic cacalol acetate[10,11].

References and notes

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b) A.van der Gen, K.Wiedhaup, J.J.Swoboda, H.C.Dunathan, and W.S.Johnson, J.Amer.Chem.Soc., 95, 2656(1973).
10) The authors are indebted to Dr. J.Romo of Universidad Nacional Autonoma de Mexico for the sample of cacalol acetate (mp 103-104°C), which, according to his communication, is easily reconvertible to cacalol ($KHCO_3$/MeOH).
11) J.W.Huffman, Clemson University U.S.A., announced the synthesis of benzyl ether of I (Abstracts of 9th International Symposium on Chemistry of Natural Products, 54A, held in Ottawa, 1974) and F.Walls, Universidad Nacional Autonoma de Mexico, has synthesized cacalol recently (Dr. J.Romo's private communication); but, neither of them still has referred to comparison with the natural product.

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